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clinician to interpret cases in human beings directly in terms of these principles. The principles referred to are recapitulated here.

1. Agents that produce rapid cerebral compression, provided they are intense enough to raise the general intracranial pressure so that the external tension on the medulla oblongata is equal to the diastolic or to the mean systemic arterial blood pressure, will produce: (a) a steady rise in blood pressure to above normal; (b) a steady decrease in pulse rate to below normal, the pulse being characterized by a bounding ("vagal") quality; (c) slow, deep and stertorous respirations, becoming Cheyne-Stokes in character; (d) vomiting; (e) headache, and (f) mental torpor, stupor and, later, coma.

2. From the pathogenic standpoint, these effects are the direct result of two factors which in any given case may act independently of each other or concomitantly: (a) ischemia of the vital medullary centers and of the brain generally, and (b) a local fall in the blood pressure of these structures, brought about by the partial or complete occlusion of the arterioles of the brain under the influence of the rising intracranial pressure. The early effect of the forces of external compression on the walls of the vessels is to increase the local blood pressure. As the external pressure increases and the lumen of the vessel is narrowed, the force of the axial stream becomes lessened, both relatively and absolutely, and the shearing resistance of the peripheral stream against the wall of the vessel becomes greater, with a resulting dissipation of the mechanical energy imparted to the blood stream by the heads of pressure (i. e., the heart and the elastic rebound of the arteries). As a consequence, the blood pressure falls in those tissue beds supplied by the compressed arterioles.

3. Death is preceded by a progressive increase in intracranial pressure, a decrease in systemic blood pressure, a racing pulse and respiratory collapse.

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G. A.: *Deutsche Chirurgie*, Stuttgart, F. Enke, 1880, no. 30, p. 341. (f) Hill, L.: *Physiology and Pathology of the Cerebral Circulation*, London, J. & A. Churchill, 1896, p. 168. (g) Kocher, T.: *Hirnerschütterung, Hirndruck und chirurgische Eingriffe bei Hirnerkrankungen*, in Nothnagel, H.: *Specielle Pathologie und Therapie*, Vienna, A. Hölder, 1901, vol. 9, p. 2. (h) Cushing, H.: *Concerning a Definite Regulatory Mechanism of the Vasomotor Centre Which Controls Blood Pressure During Cerebral Compression*, *Bull. Johns Hopkins Hosp.* **12**:290, 1901; (i) *Some Experimental and Clinical Observations Concerning States of Increased Intracranial Tension*, *Am. J. M. Sc.* **124**:375, 1902; (j) *Blood-Pressure Reaction of Acute Cerebral Compression, Illustrated by Cases of Intracranial Hemorrhage*, *ibid.* **125**:1017, 1903. (k) Cooper, A.: *Lectures on the Principles and Practice of Surgery*, London, T. & G. Underwood, 1894, vol. 1, pp. 282-313. (l) Eyster, J. A. E.; Burrows, M. T., and Essick, C. R.: *Studies on Intracranial Pressure*, *J. Exper. Med.* **2**:489, 1901. (m) Eyster, J. A. E.: *Blood Pressure Changes in Cheyne-Stokes Respiration*, *Bull. Johns Hopkins Hosp.* **17**:296, 1906.

is on the increase and (4) that death results from overstimulation of the medullary centers under the influence of a steadily rising intracranial tension.

In order to bring the question of the alleged constitutional effects of increased intracranial pressure fairly under inquiry, this factor alone, uncomplicated by any other intracerebral factors (such as may be presumed to obtain following severe trauma to the head), should be the object of study. As was noted in the previous paper of this series, it is uncommon clinically to find cerebrospinal fluid pressures as high as from 40 to 70 mm. of mercury (from 540 to 950 mm. of water), and only rarely are higher levels encountered. In the present study, as a supplement to our clinical observations in cases of injury to the brain, an attempt was made to determine experimentally in human beings the

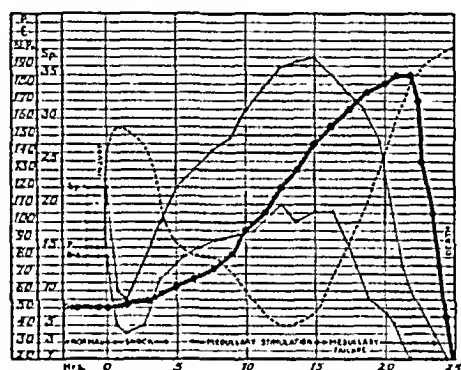


Fig. 2.—Chart illustrating the course of events following a rise in intracranial pressure according to a conception widely employed and taught in surgical practice. After recovery from the initial shock, the intracranial pressure rises and there is a *pari passu* rise in the blood pressure and fall in pulse rate until medullary failure ensues. From this point on the blood pressure falls, the pulse races and shock becomes evident, leading almost inevitably to death.

effect on the vital signs that could be produced by raising the intracranial tension to levels of a magnitude equal to or higher than the levels in cases of the most severe trauma.

#### MATERIAL AND METHOD

Ten patients, each of whom had a large operative cranial defect, were used for the observations. At the time of the study, each patient had convalesced from an exploratory operation for tumor of the brain, and it was readily possible, through the cranial defect (fig. 3), to influence the intracranial contents by the application of agents of external pressure. For purposes of control, comparable studies were carried out on three patients with intact craniums.

The standard procedure consisted in placing the patient horizontally in bed in the lateral prone position. The subject was made to lie so that the side of the

## EXPERIMENTAL STUDIES

The salient clinical features derived from a study of four of the thirteen patients<sup>4</sup> used for these experiments, together with the tables and graphs derived from the corresponding experimental data, are briefly reviewed here.

In the graphs the abscissa represents the time, and each unit interval equals one minute. In the first ordinate column may be read the pulse rate (P.) and blood pressure (Sy, Dia.) levels. Each unit represents five beats per minute, or 5 mm. of mercury, as the case may be. In the second ordinate column are read the respiratory rate (Resp.), the head

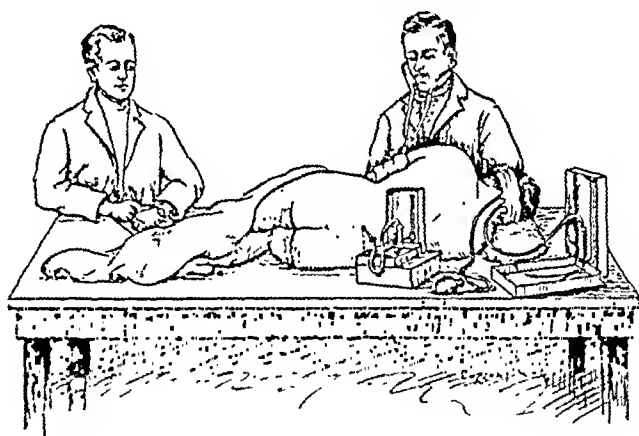
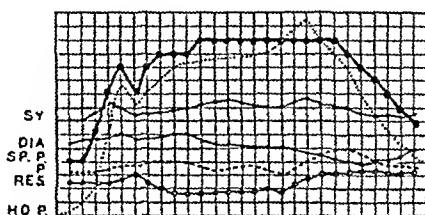


Fig. 4.—The experimental set-up employed in this study.

pressure (Hd.P.) and the cerebrospinal fluid pressure (Sp.P.) levels. The unit intervals here represent three respirations per minute, or 3 mm. of mercury, as the case may be. The curve of the pulse rate is represented by a heavy broken line. The curves for the systolic (Sy.) and diastolic (Dia.) blood pressures are in heavy black dots connected by uninterrupted narrow lines. They constitute the boundaries of a gray band which may be regarded as the pulse pressure. The curve for the respiratory rate is represented by circles and dashes, that for the

4. The data on the remaining patients have been omitted from this communication in the interest of conciseness of presentation. In their essential features, the principles illustrated in these experiments conform closely to those illustrated in the four experiments recorded here.

an operation elsewhere for the removal of a tumor of the right temporal lobe. For the succeeding two and one-half years she remained fairly free from symptoms. However, two months before her admission to the Kings County Hospital, headache, drowsiness, dizziness and defects in memory appeared and increased progressively. Vomiting occurred at times, and periods of stupor alternated with those of a lucid state. Physical examination revealed a deeply stuporous, well

TABLE 1.—Data for Experiment 1

Time, Min.	Head Pressure, Mm. of Hg	Spinal Pressure, Mm. of Hg*	Pulse Rate, per Min.	Blood Pressure, Mm. of Hg	Respiratory Rate, per Min.
Control.....	0	8.0	104	112/63	18
1.....	60	7.8	118	110/66	18
2.....	70	8.0	106	110/68	17
5.....	80	8.0	100	114/62	17
7.....	90	8.2	96	108/62	18
9.....	100	8.0	96	106/64	16
12.....	110	7.8	96	110/66	15
15.....	120	7.0	98	114/62	14
20.....	120	7.5	100	112/60	16
25.....	120	7.5	104	114/72	17
30.....	120	6.8	100	116/64	18
35.....	120	8.0	88	108/60	18
40.....	120	8.0	96	114/64	17
45.....	120	8.2	100	110/66	16
50.....	120	7.8	104	112/62	16
55.....	120	8.0	94	110/64	16
60.....	120	7.5	92	108/64	16
65.....	0	7.5	88	110/66	18

\* A water manometer was used. The figures were translated into mercury equivalents for the purpose of uniformity of record.

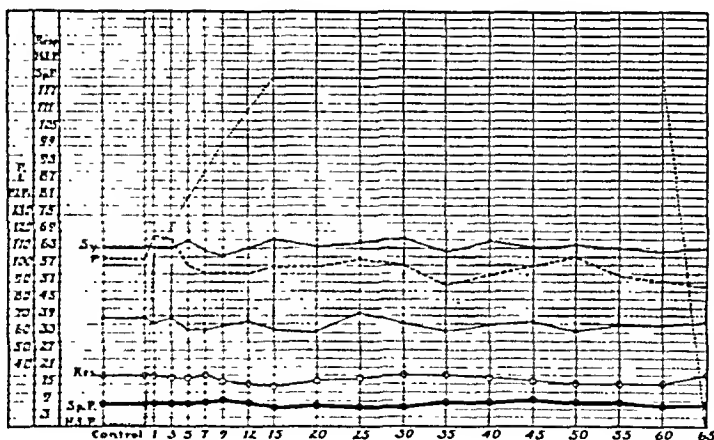


Fig. 5 (case 1).—Record of a patient with a paroxysmal convulsive disorder. This record is representative of the control group and illustrates the variations in vital signs that may be expected under conditions of the experiment.

developed and well nourished woman in early middle life. A bulging mass the size of a large plum presented within the omega-shaped operative scar on the right side of the head. Bilateral exophoria was noted, and there were slow lateral oscillations of the eyes. The pupils were equal and reacted sluggishly. Ophthalmoscopy revealed bilateral papilledema of a high degree. The abdominal reflexes were absent. There was paresis of a suprasegmental type on the left side, with a fairly sustained ankle clonus on the left and an equivocal Babinski sign on the

elevation of systemic blood pressure appeared when the second study was carried out on this patient (see table 3 and fig. 5), even though in this instance a much more severe and prompt rise in cerebrospinal fluid pressure was employed. It may be held that the emotional response related to the strangeness of the experimental set-up had largely passed off at the time of the second observation.

EXPERIMENT 2 a.—A. M., the same subject used in experiment 2, was observed a second time. The effect of an almost instantaneous rise (i. e., within thirty seconds) of the cerebrospinal fluid pressure was the matter chiefly under study. This observation was carried out two days after the first experiment, and the data are presented in table 3 and figure 7.

TABLE 3.—Data for Experiment 2 a

Time, Min.	Head Pressure, Mm. of Hg	Spinal Pressure, Mm. of Hg*	Pulse Rate, per Min.	Blood Pressure, Mm. of Hg	Respiratory Rate, per Min.
Control.....	0	20	116	118/78	28
1/2.....	52	73	112	123/84	30
1 1/2.....	52	68	111	125/82	30
2.....	..	..	...	.....	..
2 1/2.....	..	..	...	.....	..
3.....	52	65	104	122/84	28
4.....	52	62	110	124/85	28
5.....	52	60	107	116/88	30
6.....	..	..	...	.....	..
7.....	52	53	106	138/83	28
8.....	52	57	108	122/88	28
9.....	52	56	110	120/86	27
10.....	52	55	108	122/84	26
11.....	..	..	...	.....	..
12.....	..	..	...	.....	..
13.....	52	52	106	121/82	30
15.....	52	52	110	119/82	30
20.....	52	46	114	119/86	25
25.....	52	43	114	124/88	26
30.....	52	41	104	118/85	25
35.....	52	38	102	123/96	24
38.....	34	33	110	123/92	25
39.....	34	32	110	126/86	25
40.....	20	23	96	122/90	24
43.....	20	23	106	125/94	24
45.....	0	13	106	118/88	22
50.....	0	13	102	119/84	23

\* A mercury manometer was used.

The patient was feeling irritable and restive. She made no verbal complaint, but at times (starting at the twenty-fifth minute) grunted at the end of expiration and expressed impatience with the procedure.

In this experiment the effect of a sudden rapid and high rise of cerebrospinal fluid pressure was studied. No significant change in the systemic blood pressure, pulse rate or respiratory rate was observed.

EXPERIMENT 3.—J. W., a white man aged 52, was transferred to the Bellevue Hospital on March 12, 1935, from another hospital, where his condition was diagnosed as glioblastoma multiforme in the left frontotemporal region. The earliest symptoms had appeared two years before admission and consisted of transient recurrent paralysis of the right upper extremity. In December 1934 he had an episode of transient aphasia of the receptive and emissive type. Except for these symptoms, the patient felt well and was able to work until Jan. 10, 1935,

At one period bradycardia occurred, but singularly enough the blood pressure was falling at this time, even though the cerebrospinal fluid pressure was being increased. Again, at the time when the systolic blood pressure reached its highest level (150 mm. of mercury), no tendency toward bradycardia was evident, the pulse rate being 80 per minute. It is to be noted that the diastolic pressure was exceeded by the intracranial pressure between the twentieth and the sixty-fifth minute of the experiment.

TABLE 4.—Data for Experiment 3

Time, Min.	Head Pressure, Mm. of Hg	Spinal Pressure, Mm. of Hg*	Pulse Rate, per Min.	Blood Pressure, Mm. of Hg	Respiratory Rate, per Min.
Control 1.....	0	34	88	108/74	14
Control 3.....	0	34	88	108/74	14
Control 5.....	0	35	88	110/70	14
1.....	28	56	84	110/78	14
2.....	62	80	84	114/78	14
3.....	60	80	84	120/92	18
4.....	54	70	96	130/90	18
5.....	84	92	96	134/92	18
6.....	80	90	88	130/84	18
7.....	84	92	68	126/88	20
8.....	90	102	48	126/80	20
9.....	88	84	40	122/62	18
10.....	88	80	48	102/58	20
11.....	86	78	48	102/58	20
12.....	84	78	44	104/58	22
15.....	88	80	60	106/56	16
20.....	88	82	68	134/58	20
25.....	88	80	68	122/68	20
30.....	88	78	78	124/58	22
35.....	88	81	74	124/58	20
40.....	88	76	80	134/60	18
45.....	88	76	78	130/60	18
50.....	106	86	72	134/60	18
55.....	106	88	72	134/60	18
60.....	106	86	80	140/60	18
65.....	106	86	76	150/64	18
70.....	50	68	68	132/60	18
72.....	50	66	68	132/60	20
75.....	20	50	80	130/56	20
85.....	8	40	78	135/50	22
90.....	8	40	78	134/50	24
95.....	0	28†	72	130/54	24
100.....	0	20‡	80	132/60	24
105.....	0	12#	84	132/56	24

\* A mercury manometer was used.

† Fifteen cubic centimeters of cerebrospinal fluid was withdrawn.

‡ Five cubic centimeters of cerebrospinal fluid was withdrawn.

# Four cubic centimeters of cerebrospinal fluid was withdrawn.

EXPERIMENT 4.—B. A., a 39 year old white housewife, was admitted to the Kings County Hospital on Dec. 4, 1935, complaining of generalized headache, bilateral tinnitus, vomiting and progressive paresis on the left side of several months' duration. Thirteen years previous to admission she had been institutionalized for hebephrenic schizophrenia, the symptoms of which were irregularly present until the onset of her headaches. Examination revealed an oriented but distractable and at times incoherent patient with grandiose delusions, facetiousness and periodic psychomotor acceleration. Visual acuity was diminished. The visual fields could not be properly tested, but marked papilledema was present bilaterally. The left pupil was larger than the right. Paresis involving the left side of the face and the left arm and leg was evident. This was attended by the usual signs



TABLE 5.—Data for Experiment 4

Time, Min.	Head Pressure, mm. of Hg	Spinal Pressure, mm. of Hg*	Pulse Rate, per Min.	Blood Pressure, mm. of Hg	Respiratory Rate, per Min.
Control 1.....	0	32	118	118/ 92	16
Control 2.....	0	30	102	110/ 92	16
5.....	36	82	106	122/ 92	16
7.....	38	84	102	116/ 90	16
12.....	35	80	92	118/ 86	14
17.....	38	80	108	128/ 90	16
22.....	42	80	86-100	132/ 92	16
27.....	60	94	98	122/ 90	16
29.....	94	130	120	154/102	16
31.....	50	82	98	140/ 96	12
34.....	60	88	80	130/ 90	12
36.....	120	112-140	..	.....	Rapid snorting
39.....	108	126-136	140	154/118	18
40.....	111	120	136	168/118	20
43.....	114	120	144	182/118	18
44.....	64	80	66	128/ 84	18
46.....	66	82	...	.....	..
51.....	74	84	118	140/ 96	16
52.....	134	114-120	146	188/120	22
56.....	128	112-118	92	172/108	18
57.....	0	26	60	122/ 86	14
60.....	0	28	..	.....	..
62.....	0	21	68	108/ 78	12
65.....	0	20	68	100/ 74	12
70.....	0	20	76	100/ 74	14

\* A mercury manometer was used.

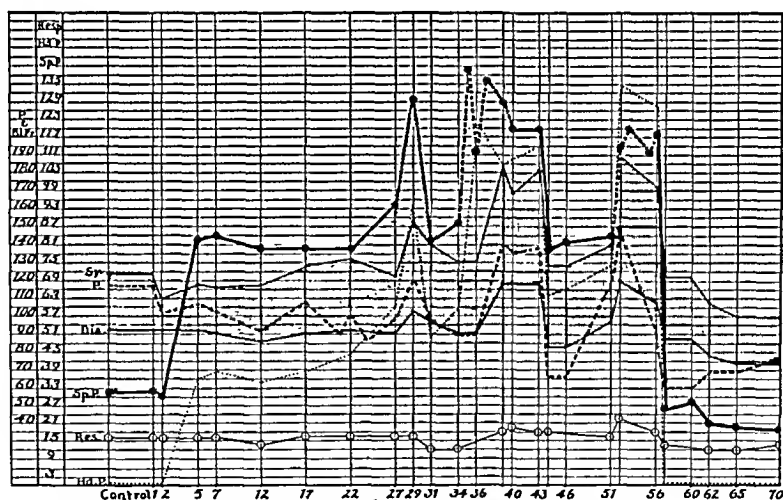


Fig. 9 (case 4).—Postoperative record of a patient with glioblastoma multiforme of the right parieto-occipital lobe. In this record the curve representing the cerebrospinal fluid pressure has been broken corresponding to periods during which the patient became restive and her respirations irregular. At these times the fluctuations of the cerebrospinal fluid pressure were so rapid as to preclude their being separately represented on the graph. However, the limits within which variations occurred are here indicated. It will be noted that the findings associated with intracranial pressure levels above 100 and 110 mm. of mercury are consistent with those reported in animal experimentation. Below these levels, only slight variations in systemic blood pressure, pulse rate and respiratory rate appeared.

cerebrospinal fluid pressure and systemic blood pressure unless the level of the former reaches the diastolic or mean blood pressure. Thus, Fremont-Smith and Merritt,<sup>74</sup> in a study of 1,606 cases, found that the levels of the diastolic and the systolic blood pressure were uninfluenced in the face of intracranial pressure up to 800 mm. of water and that the cerebrospinal fluid pressure was uninfluenced in the face of increased vascular tension by itself. These observations agreed with results published in a previous paper by Fremont-Smith and Kubie.<sup>74</sup> A number of investigators who have carried out experiments with animals had been led to similar conclusions (Becht,<sup>75</sup> Cushing,<sup>23</sup> Eyster,<sup>21</sup> Wolff and Forbes,<sup>76</sup> Weed and Hughson,<sup>77</sup> Becht and Matill<sup>78</sup>), and as a result of their clinical and experimental observations, Adson and Lillie,<sup>79</sup> Parker,<sup>72</sup> Gurdjian<sup>78</sup> and Wilson<sup>79</sup> have been able to lend their support to the same expression. Yet despite the lines of evidence advanced by these authors, the majority of practitioners continue to be guided by the notion that a rise in cerebrospinal fluid pressure per se to levels of the magnitude met in clinical practice regularly affects the systemic blood pressure and the pulse rate. According to the observations made after craniocerebral injuries, which were reported in our previous paper, the relationship between variables, viz., cerebrospinal fluid pressure, systemic blood pressure, respiratory rate and pulse rate, may assume any pattern mathematically possible. Although it may occasionally appear that the reaction on the part of the blood pressure and the pulse rate to a rapidly expanding intracranial lesion (brain trauma) conforms to the Kocher pattern, it would rarely, if ever, prove on mensuration of the cerebrospinal fluid pressure to be explicable in terms of this factor alone. This does not mean to imply that the reduction of even a mild increase in the measurable intracranial tension may not in certain instances influ-

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indicate previous infection. When routine microscopic examination is not done on appendixes removed at operation, the presence or absence of signs of inflammation can never be ascertained positively except grossly. When marked adenopathy involving a number of lymph nodes has been found at operation, with a more acute type of inflammation than is found in the appendix, no definite avenue for entrance of the infecting organism has been proved, although the theories have been many, varying from a hematogenous one<sup>19a</sup> to that of the absorption type of transmission through the intestinal mucosa.<sup>21</sup> The adherents to the theory of hematogenous infection of the mesenteric lymph nodes cannot explain the anatomic location of the nodes affected, particularly those of the ileocecal group thought to drain a definite area alone. The believers in local absorption from the intestine which drains into the nodes of the ileocecal group cannot explain fully how this absorption occurs without a demonstrable lesion in or about the intestine or how oftentimes the nodes higher up appear larger than those of the ileocecal group. Then, too, reports of bacterial investigation of appendical infections are not easy to find, though the number of bacteria which have been cultured from appendixes are multiform in examinations reported in detail.<sup>22</sup> Various unusual appendical infections from parasites, such as *Oxyuris vermicularis*, *Endamoeba histolytica* and *Ascaris*, have been described, but no one type of infection has been found associated with mesenteric adenopathy. The difficulty and the possible danger of removing lymph nodes have been mentioned. This is especially true, even though the glands are not calcified in the clinically tuberculous type of swelling and a streptococcus is the cause of the infection.

One of the soundest hypotheses about mesenteric lymphadenitis appears to be based on the general idea of a lymphatic system for the entire body, existing as a unit rather than as separate parts. Macfayden and MacConkey<sup>23</sup> in 1903 called attention to the association of mesenteric lymph nodes, the faucial tonsils and the adenoids as part of the whole lymphoid system. A list of the agents which can cause generalized adenopathy must be understood as including many others besides the following: infections of the upper respiratory tract, exanthems, typhoid, influenza, tuberculosis, syphilis, many cutaneous diseases, poisoning due to certain metals, marked inflammation or ulcers of the intestines, especially those of long duration, actinomycosis, leukemia, sarcoma, Hodgkin's disease, metastatic carcinoma, rickets, scurvy, status lymphaticus and foci of infection of various types, even intestinal stasis.

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intestinal obstruction were found, the only apparent cause being the involvement of the mesenteric lymph nodes. The appendix was not examined. No postmortem examination was done.

The third patient, a boy aged 5 years, had an operation for what was termed a "tuberculous abscess of the mesenteric gland." The result was good, and the diagnosis was verified by microscopic evidence. The condition of the appendix was not described on the chart.

Two patients were not operated on, although the diagnosis of involvement of the mesenteric lymph nodes was made. One of these was a boy of 2 years, who died of several diseases—diabetes, ulcerative lesions of the colon and ileum and an infection of the upper respiratory tract in addition to mesenteric lymphadenitis. The other patient recovered from symptoms of abdominal disease and an infection of the respiratory tract within a few days without operation.

TABLE 1.—*Distribution of Cases as to Age and Sex*

Age	Number of Cases	Males	Females
Under 1 year.....	0	0	0
1-6 (incl. 6).....	15	11	4
7-10 (incl. 10).....	31	17	14
11-16 (incl. 16).....	20	13	7
17-21 (incl. 21).....	7	3	4
22-29 (incl. 29).....	21	9	12
30-37 (incl. 37).....	6	3	3
38-72 (incl. 72).....	10	4	6
Total.....	110	60	50
Under 21.....	71	42	29
21 and over.....	39	17	22
16 and under.....	66	41	25
10 and under.....	46	28	18

Close analysis of the remaining 110 cases is helpful but must naturally be regarded reservedly, because it is true that these are cases of a most selected type. In many hundreds of other cases in which operation was done for so-called chronic appendicitis, a simultaneous diagnosis of mesenteric lymphadenitis was not made. Free abdominal exploration for swelling of the lymph nodes cannot be carried out in the presence of more acute types of appendicitis. Moreover, surgeons vary in the emphasis they place on such swellings, either while operating or later when dictating the operative findings to the surgical secretary.

With these admissions and with due credit to investigators who have suggested studies like this before, I wish to present the apparently related facts about these 110 cases of mesenteric lymphadenitis, first excluding the 8 in which the condition was associated with an intra-abdominal malignant tumor, 2 in which operation was not performed (the diagnosis in 1 of which is doubtful) and 3 in which there was no condition other than the mesenteric lymphadenopathy, 1 of these being the case of definite tuberculous abscess of a mesenteric gland.

When doubt about the classifying of lymphadenitis was felt, it was overcome by considering the case under the group of chronic infections.

In the group of 115 cases of mesenteric lymphadenitis, there were 74, or 64 per cent, in which the condition was chronic; 8, or 7 per cent, in which it was distinctly acute; 4, or 3 per cent, in which it was purulent, and 37, or 32 per cent, in which it was clinically tuberculous. Some of the cases in the last three groups overlapped in classification, as can be easily seen in the table from the unrelated percentages. The condition in 1 case could not be classified.

The 109 cases, or 95 per cent, with involvement of the appendix at some time or other is an inescapable fact and cannot be overemphasized. The 14 cases, or 12 per cent, in which there was involvement of the gallbladder was probably low for the whole group, because the gallbladder was perhaps not examined as a routine.

TABLE 3.—*Further Data on 115 Cases of Mesenteric Lymphadenitis*

Average Age	Sex	Chronic Mesenteric Lymphadenitis*	Acute Mesenteric Lymphadenitis	Purulent Mesenteric Lymphadenitis	Pronounced Olinleal Tuberculosis of Mesenteric Lymph Nodes	Associated Appendicitis at Any Time	Associated Visceroproptosis or Constipation	Fecal Material(+) or Fecalith(++) in Appendix	Associated Disease of Gallbladder at Any Time (Proved)
16.8 yr.	61 M 54 F	74 or 64%	8 or 7%	4 or 3%	37 or 32%	109 or 95%	31 or 27%	24+ or 21% 30++ or 26%	14 or 95%
								54 or 47%	

\* These percentages are of the total only and are not completely differentiating or interrelated. For example, sometimes a case is classified as one of chronic lymphadenitis as well as one of clinical tuberculosis of the mesenteric lymph nodes.

The occurrence of visceroproptosis or constipation in 31 cases, or 27 per cent, is probably also low for this group, for the reason that such facts are seldom recorded as a routine on the charts when other more evident diseases prevail.

Fecal content in the appendixes, though not always recorded perhaps, seems most significant in 24, or 21 per cent, of the cases. The additional cases, or 26 per cent, in which a fecalith was recorded swell the number to 54, or 47 per cent, in which there was tangible, positive proof of stasis in the appendix, a condition which possibly could have been responsible for a predisposition to the associated mesenteric lymphadenitis as well as to the disease of the appendix so often found.

The main symptoms and abdominal findings for the whole group of 115 cases are presented in table 4.

Indications of the truth about clinical symptomatology can be gained to some extent if the totals presented in table 4 are summed up. They reveal that vomiting occurred and was positively recorded in 58 cases, or 50 per cent of the total. Distention or tympany was recorded in only 6

ing. Of the 37 cases in which a clinical diagnosis of tuberculous mesenteric lymphadenitis was made, microscopic proof is available for only 4, or 10 per cent. Inoculation of only 1 guinea-pig was recorded, although other tests must have been done, to judge by the operative notes.

TABLE 5.—Totals in 123 Cases of Disease of the Mesenteric Lymph Nodes

Cases	Description	Operation	Death	Acute Infection	Chronic Infection	Suppurative Infection	Tuberculous Infection	Unclassified
63	Appendectomy only.....	63	2	4	48	0	11	0
47	Operation in addition to appendectomy and other diseases.....	47	5	3	26	(2)	23	0
3	Nothing recorded but mesenteric adenitis in the abdomen.....	3	1	1	0	(1)	3	0
2	No operation.....	0	1	1	0	(1)	0	1
8	Intra-abdominal malignant growth.....	8	8 (presumably)	1	7	(1)	0	0
123	.....	121 or 98%	17 or 14%	10 or 8%	81 or 66%	(5) or 4%	37 or 32%	1 or 0.8%

TABLE 6.—Involvement of Appendix in 123 Cases of Disease of the Mesenteric Lymph Nodes, 1914 to Aug. 1, 1936

Cases	Description	Gross Acute or Chronic Appendiceal Involvement at Same Time (On Admission)	Appendectomy at Some Time	Previous Appendectomy	Appendectomy Done at Present Admission	Later Appendectomy	Positive Microscopic Evidence of Appendiceal Involvement Past or Present Admission
63	Appendectomy only....	63	63	0	63	0	62
47	Operations in addition to appendectomy and other diseases.....	41	44	3	41	0	41
3	Nothing recorded but mesenteric adenitis in the abdomen.....	0	1 (9 yr. later)	0	0	1	1
2	No operation.....	0	0	0	0	0	0
8	Intra-abdominal cancer	2	3	1	2	0	3
123	.....	106 or 86%	111 or 90%	4 or 3%	106 or 86%	1 or 0.8%	107 or 87%

To conclude the tabulation of the entire series so as to include all the cases of involvement of the mesenteric lymph nodes from 1914 to Aug. 1, 1936, it is necessary to consider the 8 other cases—besides the 115 so far studied—in which malignant neoplasms were present in the abdomen. Briefly, the cases are divided so as to show the total percentages (table 5).

The data in tables 5 and 6 are self-explanatory and serve to increase the evidence that gives the appendix a major place in the diagnosis and

which is elective in the nose and throat, but a moment's consideration will show that such physicians are insufficiently concerned about the patients in the cities where hygiene is at low ebb and where little sunlight, fresh air and decreased outdoor exercise are the rule for the majority.

A large number of investigators, including Andersen,<sup>28</sup> Auguy,<sup>29</sup> Bell,<sup>18</sup> Bonjour,<sup>30</sup> Bose,<sup>31</sup> Braithwaite,<sup>24d</sup> Brown,<sup>32</sup> Cave,<sup>25</sup> Coleman,<sup>33</sup> Corner,<sup>34</sup> du Bourguet and Roquigny,<sup>35</sup> Duteil,<sup>36</sup> Duval and Roux,<sup>37</sup> Felsen,<sup>38</sup> Ferry,<sup>39</sup> Goldberg and Nathanson,<sup>19a</sup> Goldschmidt,<sup>40</sup> Karger,<sup>41</sup> Lamson,<sup>42</sup> Marchant,<sup>20</sup> McFadden,<sup>43</sup> Levin,<sup>44</sup> Lund,<sup>45</sup> Mead,<sup>3</sup> Neuer,<sup>46</sup>

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29. Auguy, J.: De l'adénopathie appendiculaire, Thèse de Lyon, no. 134, 1901.

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The various possible complications of mesenteric lymphadenitis need only to be mentioned to impress the reader with the great significance they may assume in the disease: obstruction of the common duct, duodenal obstruction, arroision of the mesenteric artery with resulting hemorrhage, thrombosis of the mesenteric vessels, mesenteric pyemia and suppuration, intestinal obstruction, rupture causing general peritonitis or tuberculosis peritonitis, the formation of a fistula; loose bodies in the peritoneal cavity, compression of ureters, hernia from possible overstraining when pain or partial obstruction is present, miliary tuberculosis, abscess of the psoas muscle or abscess pointing through Petit's triangle, abscess of the liver, subdiaphragmatic abscess and cholecystitis and chronic hepatitis.

Should there not be, then, a greater interest in the mesenteric lymph nodes, and can there not be and should there not be a routine recording of their condition, not only at postmortem examination, but also on the living person at every laparotomy?

Since both Alvarez and Heyd emphasize the importance of the work of Adami, who stressed autointoxication and subinfection from the bowel twenty-two years ago, there must be a reason for their not discarding this belief.<sup>60</sup> Just why it is that in certain cases visceroptosis, constipation and stasis are accompanied by mesenteric lymphangitis is not known.<sup>61</sup> Why these conditions could allow, predispose to or possibly incite mesenteric adenopathy is not known. Nor is it known what stimulates the onset of Hodgkin's disease or leukemia, unless it is a virus or activation from some infective process of the upper respiratory tract. Perhaps the relation of the nervous system to chronic appendicitis should be thought paramount to any other predisposing causes, when one considers that Kobre attributed chronic appendicitis to a disturbance of the sympathetic nervous system.<sup>62</sup> Again, Hosoi's finding of neuromas in 82 per cent of obliterated appendixes seems interesting if not pertinent in this connection.<sup>26</sup>

Here a most interesting fact may aid in a partial solution of this problem. Bezecny<sup>63</sup> in 1933 reported the finding of a histamine-like

60. (a) Heyd, C. G.; MacNeal, W. J., and Killian, J. A.: Hepatitis in Its Relation to Inflammatory Disease of the Abdomen: A Clinical and Laboratory Study, *Am. J. Obst. & Gynec.* **7**:413-430 (April) 1924. (b) Heyd, C. G.: The Liver and Gall-Bladder Disease, *New York State J. Med.* **36**:974-978 (July 1) 1936. (c) Alvarez.<sup>10</sup> (d) Heyd.<sup>5</sup>

61. Brian, P.: Les adénopathies mesenteriques et la stase intestinale, Thèse de Paris, 1925. Connell.<sup>10b</sup>

62. Kobre, M.: So-Called Primary Chronic Appendicitis as Manifestation of Disturbance of Sympathetic Nervous System, *Norsk mag. f. lægevidensk.* **94**:856-886 (Aug.) 1933.

63. Bezecny, R.: Histamin und Lymphgefäss, *Arch. f. Dermat. u. Syph.* **167**: 386-393 (Jan. 20) 1933.



than constipation. The temperature, the pulse rate, and the leukocyte count may all be normal or practically so. The question is to try to decide on a diagnosis, if possible, regardless of editorials and original contributions which mention that it is difficult. In one group of the 123 cases analyzed—the 63 in which simple appendectomy alone was performed—there were 4 cases, or 6 per cent, in which the diagnosis of mesenteric lymphadenitis was made preoperatively. In the group of 47 there were possibly 2 cases, or 4 per cent, in which the diagnosis was made before operation. That makes about 5 per cent of the 123 unselected cases in which the correct diagnosis was made preoperatively.

Regardless of the fact that operation will reveal the diseased glands, one should try to diagnose the condition preoperatively to the best of one's ability. Obviously the most important suggestions for better diagnosis are a complete history and physical examination. By a complete history is meant one that is obtained by a clearly defined plan of interrogating the patient, or family when necessary, for positive and not for negative facts. The particular points to look for are family background, especially for tuberculosis, dysentery and parasitic, exanthematous, syphilitic and metabolic diseases, and next, for a past history of tonsillitis, sore throat, exanthems, severe sinus infections or carious teeth, disease of the middle ear, food poisoning, typhoid, dysentery and the taking of cathartics. — Occupation, habits and marital history may offer considerable enlightenment, if there is evidence of repeated miscarriages, sterility and abnormal children. The amount of exercise at the time the patient is seen compared with what was habitual previously might offer an aid to the diagnosis of gastro-intestinal stasis. The same might be said of increased weight, overeating and other such suggestive findings.

In the entire series of cases, including those of intra-abdominal malignant neoplasm, recurrent symptoms were positively recorded before those complained of on admission in 92 cases, or 80 per cent. Again one should remember the number of cases in the total series of 123 in which there was evidence of disease of the appendix at some time or other, namely, 111 cases, or 90 per cent. Why, then, should these recurrent symptoms be attributed entirely to the mesenteric lymph nodes?

One should keep in mind recurrent symptoms, foci of disease in the upper respiratory tract, constipation, visceroptosis and acute and chronic appendicitis with associated mesenteric lymphadenitis and perhaps in the future the diagnosis of mesenteric lymphadenitis can often be made preoperatively. It goes without saying that the absolute diagnosis of visceroptosis in, commonly, a thin, pssthenic adolescent of sedentary, unhealthy habits must be left to the roentgenologist. The presumptive diagnosis is usually simple to make. Constipation should not be diagnosed without the explanation to the patient first that by constipation is

of a typical history of appendicitis—one should think of a diagnosis of mesenteric lymphadenitis. If, in addition to normally expected signs of acute appendicitis, a spastic sphincter ani or visceroptosis is obvious, or a hard stool is palpable, one should again think of a diagnosis of mesenteric lymphadenitis. This does not mean that appendicitis should necessarily be omitted from simultaneous consideration or that the operation should be postponed. No diagnosis is intended to be recommended which causes delay and resulting morbidity from neglected appendicitis.

If there are any positive signs of disease of the gallbladder or gallstones, tenderness in the region of the liver, with a history of indigestion, gas and other typical manifestations, in addition to the symptoms lower in the abdomen, and a diagnosis of appendicitis or mesenteric lymphadenitis is being considered, these two conditions should not be omitted from the preoperative diagnosis or impression because of the predominance of symptoms in the upper part of the abdomen.

Laboratory findings, when positive, are of great help in pointing to mesenteric lymphadenitis. No one positive laboratory test is absolute, however, although in skilled hands a roentgenogram may often show calcified abdominal lymph nodes, especially if roentgenograms are made as a routine. This finding applies to the tuberculous type of mesenteric lymphadenitis in most cases anyway.

Further, tests for *Ascaris*, *Oxyuris vermicularis* and *Endamoeba histolytica* are indicated whenever possible, but even when these organisms are found they do not constitute a uniform proof of mesenteric lymphadenitis. Lewis and others have stated that since undulant fever is now known to be associated at times with mesenteric lymphadenitis, in cases in which it is suspected by the symptoms and the fever curve, agglutination tests for the organisms of the *melitensis* group are recommended.<sup>64</sup> The Widal test, cultures of material from the throat, nose and teeth and the Wasserman and Kahn tests all have a place in diagnosis which should not be minimized.

One of the most interesting tests on which all kinds of opinions can be obtained is the tuberculin test. I hesitate to enter on a discussion of it, but for the sake of possible help a few hints are given. There are various tuberculin tests which can be used. The Mantoux test is well recognized and probably gives as good results as any. A positive reaction to this test has little significance, however, in any but the youngest children—arbitrarily, say, aged 5 or under. Even then it may not indicate a tuberculous infection unless the infection is the first one or the test is done a certain time after the onset of the first infection. A negative reaction, however, which is repeated in a day or two in a person

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## TREATMENT

The treatment of mesenteric lymphadenitis must depend entirely on the general attitude the surgeon takes toward infections of the lymph nodes and on the degree of inflammation found.

It is my belief that the three factors of (1) infection from the gastro-intestinal tract, (2) absorption of histamine-like products of decomposition from the intestines and (3) damaged hepatic function may lead to mesenteric lymphadenitis. The treatment depends on which of these factors appears to be the exciting cause or the most outstanding predisposing element.

The operative treatment needs little explanation further than that suggested by numerous others except that the disease should be recognized and classified definitely at operation and that appendectomy be immediately performed. Preoperative diagnosis is rare, so that the diagnosis at operation is often a surprise. The raising of the ileum into the wound so as to expose the intestine to the air is advised for the purpose perhaps of changing the oxygen tension of the intestinal wall. This has helped in tuberculous peritonitis and other tuberculous abdominal conditions. It seems to help whether tuberculosis is diagnosed or not and should be done until a hyperemia appears in the wall of the intestine. The treatment of frankly caseous lymph nodes needs no description beyond that given in many other articles. The spreading infection through the abdominal cavity from ruptured mesenteric lymph nodes should be treated according to conservative surgical principles. If the process does not appear localized or it seems that evacuation of profuse purulent material is needed, drainage should be done. If a drier, localized, caseous mass seems operable, one should not operate to remove it in its entirety without realizing that an extensive resection of small intestine may be necessary before the operation is completed, because the mesenteric vessels are so intimately and firmly adherent to such masses. It is possible, at times, to remove certain offending mesenteric lymph nodes without embarrassing the intestinal circulation. If resection of any part of the intestine seems inevitable in the cases of serious involvement that may or may not be tuberculous, it is best to do an entero-enterostomy immediately and close the wound without drainage. There is seldom need for these procedures in any but frankly tuberculous involvement.

In almost all cases no further procedure other than appendectomy without drainage is necessary unless the condition of the appendix indicates that drainage would be safer. Biopsy of the glands is needed largely for an addition to knowledge and seldom for therapeutics. It is dangerous when there is even slight likelihood of a streptococcic infection being present.

Associated conditions which were particularly noteworthy included visceroptosis, constipation and disease of the gallbladder and in 8 cases intra-abdominal malignant tumor.

The history of recurrent symptoms is so common in this series that it probably deserves a place among the marked points favoring a diagnosis of mesenteric lymphadenitis.

Although conclusions may be somewhat speculative, I believe that benefit can be gained from the detailed analyses of 123 cases herein reported with regard to clinical symptoms, findings, diagnosis and mortality.

Among the cases of mesenteric lymphadenitis in which there was little beyond involvement of the appendix, there were several in which the appendix contained fecal material or a fecalith and at times the *Oxyuris vermicularis*.

It is probably not an altogether safe procedure to remove a mesenteric lymph node.

Appendectomy or any other procedure necessary to remove abnormalities which may have had something to do with the occurrence of mesenteric lymphadenitis is the prescribed treatment.

From clinical and experimental reports in the literature, it seems probable that the tremendous importance of the mesenteric lymph nodes has been underestimated in the role that they play in infections of the gastro-intestinal tract and in generalized diseases.

The suggestion appears fitting that intestinal stasis and the conditions contributing to it allow chronic absorption of histamine-like substances which can cause mesenteric lymphadenitis, especially when the appendix is abnormal. Bacterial sensitivity in the gastro-intestinal tract is probably not sufficiently appreciated, may possibly be caused in part by the appendix and may offer a new line of approach toward future immunization and therapy.

#### SUMMARY

An attempt is made to focus attention on the importance of the function of the mesenteric lymph nodes in absorbing infection from the intestinal tract.

Of the 123 cases of disease of the mesenteric lymph nodes found in a twenty-two year period, an increasing number is noted in which a diagnosis of mesenteric lymphadenitis was made, especially during the past few years. The diagnoses in the 115 cases particularly studied were made by sixteen surgeons on the same staff. Important clinical features, symptoms, findings and mortality figures are given in detail in the different tables, with a discussion of each table immediately following its presentation.

Diagnosis is briefly touched on to emphasize, if possible, in a general way what is needed to increase the number of cases in which it

# PRODUCTION OF OSTEOSARCOMA IN A MOUSE BY THE INTRAMEDULLARY INJECTION OF 1,2-BENZOPYRENE

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AND

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Primary malignant neoplasms of bone have been produced experimentally by irradiation. Schürch<sup>1</sup> induced an osteosarcoma in the mandible of a rabbit by the application of a radium needle directly to the cortical surface. Lüdin<sup>2</sup> produced a chondrosarcoma in the tibia of a rabbit by repeated exposures to the roentgen rays (total dose, 8,000 roentgens). Schürch and Uehlinger<sup>1</sup> produced three ossifying sarcomas of the femur in rabbits by intra-osseous injections of minute quantities of radium salts. Widespread ossifying metastases in the lungs, spleen, liver and lymph nodes were observed. In two other animals nonossifying fibrosarcomas of bone developed. Daels<sup>3</sup> and Sabin, Doan and Forkner<sup>4</sup> also produced fibrosarcoma of bone in animals by means of radioactive substances.

In Martland's<sup>5</sup> series of patients who were poisoned by the prolonged ingestion of radioactive material, which accumulated in the skeleton, nonossifying fibrosarcomas of bone developed. These instances constitute experiments in man comparable to the experiments in animals just cited.

Apparently little work has been done on the possible effects of carcinogenic chemicals on the skeletal system. Woglom<sup>6</sup> and Seelig and

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This work was facilitated by a grant from the Cancer Research Institute of the Chicago Womans' Club.

From the Department of Surgery and Division of Roentgenology of the Department of Medicine, University of Chicago.

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5. Martland, H. S., and Humphries, R. E.: *Osteogenic Sarcoma in Dial Painters Using Luminous Paint*, *Arch. Path.* **7**:406 (March) 1929.
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knee joint, and the inferior articular surface of the femur was exposed. A sharp probe was inserted upward into the shaft, and crystals of 1,2-benzpyrene were pressed into the medullary cavity through these holes. Some of the crystals adhered to the surrounding muscles. The wounds were closed by interrupted silk sutures. Of eight of this group that survived from four to six months, spindle cell sarcomas developed in four in the lower part of the thigh surrounding the shaft of the femur. The latter was not extensively eroded. The tumors did not arise primarily in the bone but were sarcomas of the soft tissue.

In the remaining twelve animals a similar procedure was carried out, except that small cylinders of cholesterol from 4 to 5 mm. long and 1 mm. or less in diameter and containing 1,2-benzpyrene (10 per cent by weight) were inserted into the medullary cavity of the femur. In one instance the shaft of the femur was split by insertion of the probe, and in addition to placing a cylinder of cholesterol in the fractured shaft the probe was inserted into the tibial shaft through the upper articular surface; small fragments of cholesterol and benz-

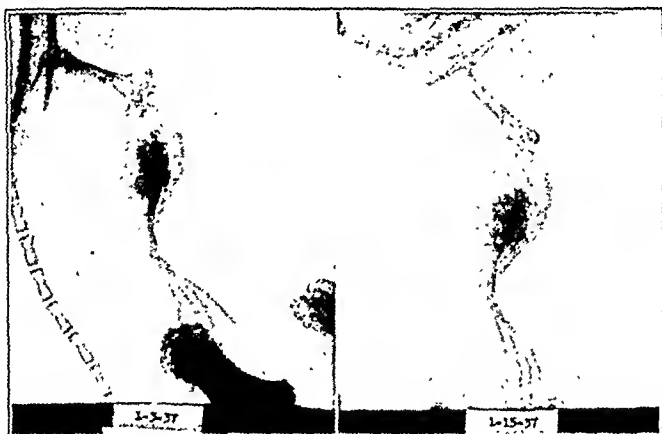


Fig. 1.—Roentgenograms of an osteosarcoma in the tibia of a mouse induced by intramedullary implantation of a mixture of 10 per cent benzpyrene and cholesterol. There was increased new bone formation in the tumor during the twelve day interval between roentgenographic examinations.

pyrene were rammed downward into the tibia. Three animals of this group survived from eight to nine months. Sarcoma did not develop in two. A hard fusiform swelling developed in the tibia of the animal which had also received a tibial implant; the swelling was more pronounced about the upper portion where the concentration of benzpyrene was greatest. Roentgenograms (fig. 1) showed irregular mottling due to new bone formation in the swelling about the tibia. The appearance was characteristic of a primary osteosarcoma. During the subsequent three weeks the swelling increased in size, and another series of roentgenograms showed considerable increase in the amount of new tumor bone. The lungs appeared clear. By this time the animal suddenly became ill and apathetic, and respirations were labored. Because transplantation of the tumor was to be carried out, the animal was then killed, although it was planned to

surrounded by necrotic spindle cells. These areas also presented varying degrees of polymorphonuclear infiltration. The peripheral margin of the tumor mass was smooth and circumscribed. The overlying muscles had been pushed outward and were only slightly infiltrated by tumor. The density of the new tumor bone varied from one portion of the section to the other. The fibula had been pushed outward for some distance from the tibia but was also included in the mass. Examination of the liver showed diffuse acute pericholangitis and curious scattered areas of coagulation necrosis of the liver cells.

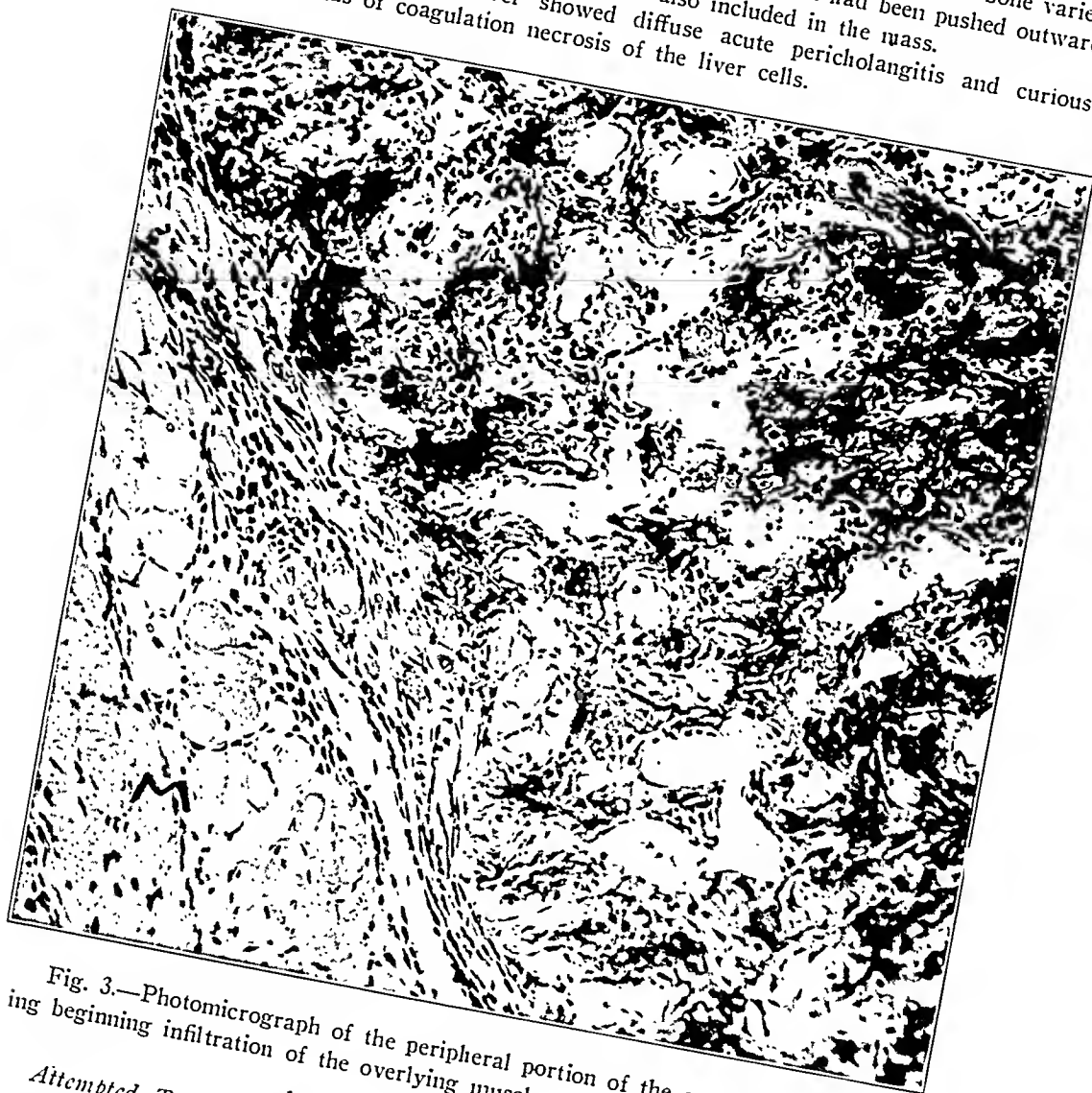


Fig. 3.—Photomicrograph of the peripheral portion of the osteosarcoma, showing beginning infiltration of the overlying muscles at *M*;  $\times 250$ .

*Attempted Transplantation.*—As stated previously, the tumor-bearing animal suddenly became ill about forty-eight hours prior to being killed. Twelve white mice in apparent good health were inoculated with fragments of the tumor by means of a trocar inserted into the subcutaneous tissues of the back and intramuscularly in the thighs. During the following ten days nine of the animals sickened rapidly and died. The livers exhibited the same gross and microscopic appearance as the liver of the tumor-bearing animal. In the surviving three mice

Because epidermoid carcinomas are produced when these compounds are applied to the skin and sarcomas develop after subcutaneous injections, it has been inferred that these hydrocarbons can produce any type of malignant tumor, depending on the tissues adequately exposed. However, final confirmation of this view must await further experimentation.

#### SUMMARY

An osteosarcoma (bone-forming sarcoma) developed in the tibia of a mouse which had received an intramedullary implantation of a mix-

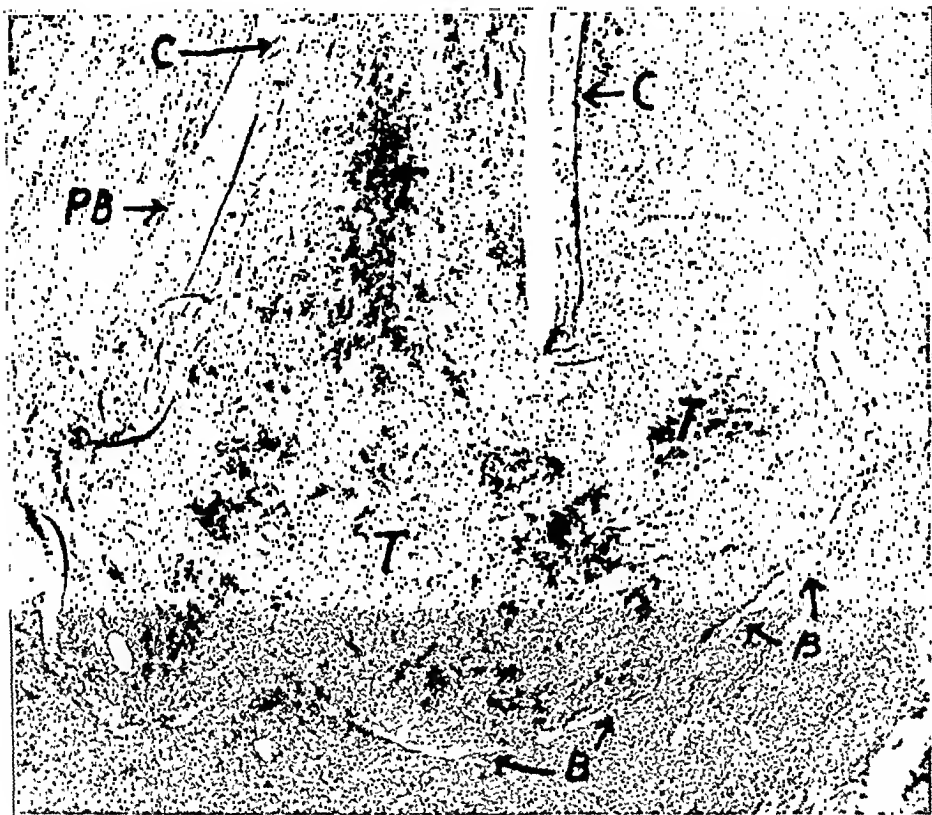


Fig. 5.—Low power photomicrograph of the lesion shown in figure 4. The tumor is composed of small spindle cells, and there is no ossification of the mass. Practically all of the lower epiphysis of the femur and some of the metaphysis have been destroyed by the tumor. *C* indicates the cortex of the lower metaphysis; *PB*, new periosteal bone—"periosteal lipping"; *T*, fibrosarcoma, and *B*, small fragments of undestroyed bone and articular cartilage pushed out of place by expansile growth of the tumor.

ture of 1,2-benzpyrene and cholesterol eight and one-half months previously. It would appear that this is the first instance recorded of the experimental production of an osteosarcoma by a chemical agent. Previously osteosarcoma and fibrosarcoma of bone have been produced experimentally only by irradiation.



# THE NICOLA OPERATION FOR RECURRENT DIS- LOCATION OF THE SHOULDER

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Because the older operations of capsulorrhaphy and Clairmont's muscle sling procedure for recurrent dislocation of the shoulder have not proved satisfactory; tenosuspensions have become a welcome substitute. Of these, the Nicola<sup>1</sup> procedure is likely to prove the best, because the operation, which consists of a suspension of the head of the humerus by passing the tendon of the long head of the biceps muscle through it, is sound anatomically and simple to perform. The modification herein suggested is designed to facilitate conducting the tendon through a newly formed channel in the head of the humerus and also to insure a snug relationship between the two, which is one of the most important details in preventing recurrence of the dislocation.

To insure uniformly good results from this operation, certain technical details must be rigidly adhered to. These are as follows:

1. The channel through the head of the humerus must begin in the bicipital groove about 1 inch (2.5 cm.) below the lesser tuberosity. It must run a course so that its other end will appear on the articular head of the humerus (in the line of direction of the long tendon) about  $\frac{1}{2}$  to  $\frac{3}{4}$  inch (1.3 to 1.9 cm.) from the edge of the articular cartilage. This provides a maximum check to recurrent dislocation.

2. The tendon must become fixed in the tunnel in the head of the humerus after it is transplanted. To assure such fixation it is necessary that the tendon fit the channel snugly and that it be divested of synovial membrane; otherwise the tendon will slide ~~in~~ the channel and fray or wear until it breaks.

The incision is made from the clavicle just above the coracoid process downward in the line of the fibers of the deltoid muscle along its anterior margin for about 4 inches (10 cm.). The fibers are divided by blunt dissection down to the joint. The tendon of the long head of the biceps muscle is located and exposed by cutting the transverse ligament of the humerus which holds it in the groove. It is exposed completely up into the shoulder joint and downward to the upper edge of the tendon of the pectoralis major muscle as it is inserted on the external bicipital ridge, and the synovial membrane covering it is removed.

The elbow is flexed to an angle of 45 degrees and the long head of the biceps muscle is cut in a Z fashion  $\frac{1}{2}$  inch (1.3 cm.) above the point where it disappears

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From the Surgical Service of the Crown Heights Hospital.

1. Nicola, T.: Recurrent Dislocation of the Shoulder, Surg., Gynec. & Obst. 60:545-546 (Feb.) 1935.

at the point of its emergence from the drill hole. He also suggested the Z-shaped section of the tendon instead of the original transverse cut. Both of these additional precautions seem worth while.

To date the literature contains reference to thirty-seven operations by Nicola with only one recurrence and ten operations by Willard<sup>2</sup> with one recurrence. Hobart<sup>3</sup> published reports of two cases in which a combination of the Nicola and Clairmont operations was used. Without any evidence he stated that the Nicola procedure has not proved to be sufficient in all cases of severe strain.

D'Harcourt and Cuadrado<sup>4</sup> presented an extensive review of the whole subject of habitual dislocation of the shoulder and described in detail the various types of operative technic for its cure. Among them

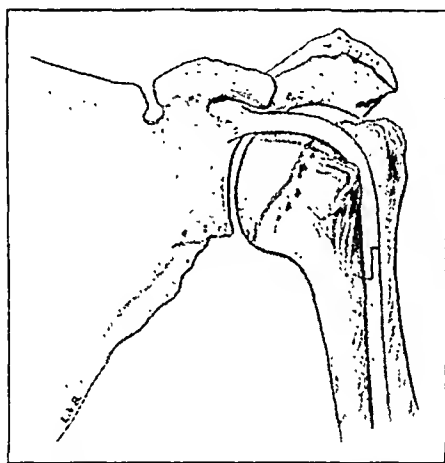


Fig. 2.—Exposure of the tendon after division of the transverse ligament. The tendon was divided  $\frac{1}{2}$  inch (1.3 cm.) above where it disappears behind the tendon of the pectoralis major muscle.

they mentioned the Nicola operation but did not report any cases of their own. Norman<sup>5</sup> described the Nicola operation and mentioned that he used it in one case, but sufficient time has not elapsed for a conclusion to be drawn.

The operation as described here has been employed in three cases. While the operations were performed so recently that the end-results

3. Hobart, M. H.: Recurrent Dislocation of the Shoulder: Nicola Operation, with Report of Cases, *J. Bone & Joint Surg.* **15**:733-736 (July) 1933; The Hobart Operation: A New Combination Operation for Recurrent Dislocation of the Shoulder, *ibid.* **17**:1001-1004 (Oct.) 1935.

4. d'Harcourt, J., and Pérez Cuadrado, F.: Contribución al estudio de la luxación habitual de hombro, *Rev. españ. de cir.* **16**:173-201 (May-June) 1934.

5. Norman, J. S.: Recurrent Dislocation of the Shoulder, *Colorado Med.* **31**:85-86 (March) 1934.

cannot as yet be estimated, it seems significant that in case 1 there has been no recurrence, despite the many epileptic attacks the patient has had since operation.

#### REPORTS OF CASES

CASE 1.—M. P., a man aged 24, was admitted to the hospital on May 4, 1936, complaining of recurrent dislocations of the left shoulder. For the past four years he had been subject to epileptic attacks with unconsciousness. The attacks usually came on in the morning when he was asleep, but occasionally they occurred during the day, at which time there was no aura. The attacks lasted a few minutes. In the two years prior to admission the left shoulder had been dislocated eight times during the attacks. Operation was performed on May 5 according to the method described. At the time this report was written there had been no recurrence, despite the continuance of the frequent attacks of epilepsy, and the patient had full range of motion.

CASE 2.—P. R., a man aged 23, was admitted to the hospital on July 21, 1936, complaining of recurrent dislocations of the left shoulder. The first dislocation occurred seven years previously. Since then, there had been six dislocations. The last one occurred the day before admission and was reduced at the St. Vincent's Hospital. Operation was performed on July 22 at the Crown Heights Hospital according to the method described. At the time this report was written there had been no recurrence, and the patient had full range of motion.

CASE 3.—J. B., a man aged 20, was admitted to the hospital on Oct. 25, 1936, complaining of recurrent dislocation of the right shoulder. The first dislocation occurred about two months previously. Subsequently two more dislocations occurred, the last one taking place two days before admission. Operation was performed on October 26 according to the method described. The patient obtained full range of motion.

Of the total patients seen, 88 appeared to the admitting physician to be in a sufficiently severe condition to warrant their admission to the hospital. The 88 hospitalized patients, together with the 17 seen in the outpatient department, make a total of 105 patients whose individual records were subjected to critical analysis.

#### HISTORICAL REVIEW

Ingested foreign bodies have played strange roles in the history of individuals and in the history of medicine. A shoe buckle came close to changing the history of the world. It was swallowed by Frederick Wilhelm I, in his fifth year on Dec. 31, 1692, and after an uneventful passage through his gastro-intestinal canal, it still lies in the Hohenzollern Museum at the Chateau of Monbijon. It was "a small silver buckle, one inch long, with the prong well protected by lying against the loop and at the other end a round knob wherewith to fix it to the strap—a very ordinary buckle, but had it not passed the larynx no Frederick the Great might have been begotten and the history of Europe would have been changed."<sup>2</sup>

The first appendectomy performed on a human subject was reported by Claudius Amyand in 1735. The patient, a boy of 11, had a discharging sinus of the right thigh which evidently communicated with an irreducible scrotal hernia. "On the interior of the hernia lay the appendix caeci which had been perforated by the point of a pin. The head, covered with much encrusted stone, remained within the appendix, acting as a ball-valve and allowing, at the most unexpected and inopportune moments, a copious discharge of fecal matter over the field of operation."<sup>1</sup> Mestivier<sup>3</sup> in 1759 is reported to have drained an abscess produced by a pin which had perforated the tip of the appendix.

The first gastrotomy for an ingested foreign body was reported by Mathis in 1602. A professional juggler, a man aged 36, had swallowed a knife, which remained in the stomach fifty-one days, causing "no great inconvenience." Adhesions between the stomach and the anterior abdominal wall were produced by "irritant plasters," and the knife was extracted through an incision made in this area.<sup>4</sup> Since then numerous reports have appeared in the literature describing remarkable

2. Layton, T. B.: Historic Foreign Body, *Brit. M. J.* **1**:24 (Jan. 4) 1930.

3. Mestivier, cited by Eitel, G. D.: Ingested Foreign Bodies in the Gastro-Intestinal Tract Requiring Surgical Removal, *Minnesota Med.* **18**:52-59 (Jan.) 1935.

4. Friedenwald, Julius, and Rosenthal, L. J.: A Statistical Report of Gastrotomies for Removal of Foreign Bodies from the Stomach, *New York M. J.* **78**:110-122, 1903.

## ETIOLOGY OF SWALLOWED FOREIGN BODIES

Carelessness, as pointed out by Chevalier Jackson,<sup>7</sup> is the most frequent etiologic agent in the swallowing or aspiration of a foreign body. Carelessness in allowing ingestible foreign bodies to lie within reach of children, together with the bad example set by mothers and nurses of putting safety pins in the mouth during the dressing hour, are responsible for the majority of ingested foreign bodies in infants and young children. Dentures which cover much of the sensitive area of the mouth and allow a foreign body to be swallowed unwittingly with the food are responsible for many of the cases seen among adults. Multiple foreign bodies in the gastro-intestinal tract are usually seen in insane persons or have been swallowed with suicidal intent.

Achlorhydria is an important etiologic agent in the production of pathologic changes due to a swallowed bone. Knud Faber<sup>8</sup> found bones in the stool of 12 patients with achlorhydria after they had eaten fish. No bones were found in the stool of persons with normal gastric acidity after a similar meal, and he therefore concluded that small bones swallowed with the food are normally digested before damage can be done to the gastro-intestinal tract. Warbasse's case<sup>9</sup> lends support to this observation. The pearl and bone handles of 7 pocket knives removed from the stomach of a professional "human ostrich" were found to have been digested. Of the cases seen at the Boston City Hospital, asymptomatic achlorhydria was found in 1—case 1, in which the stomach had been perforated by a chicken bone.

## FOREIGN BODIES PASSED PER VIAS NATURALES

The vast majority of foreign bodies ingested pass through the gastro-intestinal canal without producing symptoms or demonstrable pathologic change. Of the 800 cases seen at the Boston City Hospital, perforation occurred in only 9—an incidence of about 1 per cent. That the incidence of perforation is much less than is represented by this figure is evident when one realizes that a great many persons who have ingested a foreign body never come under the observation of the physician, either because the fact that the foreign body has been swallowed is not appreciated by the patient or because the lack of symptoms makes the consultation with a physician seem unnecessary.

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7. Jackson, Chevalier, and Jackson, Chevalier L.: *Diseases of the Air and Food Passages of Foreign Body Origin*, Philadelphia, W. B. Saunders Company, 1936, pp. 272-282.

8. Faber, Knud, cited by Norinder, E.: *Zur Kenntnis der Komplikationen bei Fremdkörpern im Magen (Ein Fall von perforierender Fischgräte)*, *Acta chir. Scandinav.* **76**:136-146, 1935.

9. Warbasse, James P.: *Tetany, and Foreign Bodies in the Stomach*, *Ann. Surg.* **40**:909-915, 1904.

of the frequency with which it is seen and its peculiar physical properties, the open safety pin is considered as a separate group. As will be seen, the nonsharp foreign bodies required an average of four and eight-tenths days to traverse the gastro-intestinal tract; those pointed at one end only required an average of five and eight-tenths days, while those

TABLE 1.—*Time Required for Passage of Foreign Bodies per Via Naturales*

Type of Foreign Body	No. of Cases	Average Age	Extremes of Age		Time Required to Pass		
			Youngest	Eldest	Average	Shortest (Age)	Longest (Age)
Straight pin.....	15	14.1 yr.	10.0 mo.	28 yr.	3.5 days	1 day (10 mo.)	7 days (1.8 mo.)
Open safety pin.....	11	4.4 yr.	9.0 mo.	12 yr.	4.6 days	1.5 days (10 mo.)	7 days (18 and 5 yr.) (2 cases)
Coin (1, 5 and 25 cent).....	11	5.4 yr.	2.0 yr.	9 yr.	4.0 days	3 days (6 yr.)	5 days (5 yr.)
Nail.....	7	5.9 yr.	1.5 yr.	10 yr.	12.0 days	3 days (10 yr.)	37 days (2.5 yr.)
Nail.....	7	6.8 yr.	4.0 mo.	35 yr.	5.3 days	5 days (4 cases)	6 days (2 cases)
Closed safety pin.....	6	3.8 yr.	2.0 mo.	8 yr.	5.3 days	3 days (2 mo.)	7 days (2 yr.)
Screw.....	3	4.0 yr.	2.0 yr.	6 yr.	2.5 days	1 day (2 yr.)	4 days (4 yr.)
Marble.....	3	6.0 yr.	4.0 yr.	7 yr.	6.5 days	6 days (7 days)	7 days (4 yr.)
Sharp glass (fragments)....	3	15.8 yr.	1.5 yr.	39 yr.	2.0 days	2 days (7 yr.)	2 days (39 yr.)
Needle.....	3	21.0 yr.	4.0 yr.	38 yr.	7.0 days	4 days (4 yr.)	10 days (21 yr.)
Pen point.....	2	4.8 yr.	0.5 yr.	9 yr.	5.0 days	5 days (9 yr.)	5 days (0.5 yr.)
Staple.....	2	4.0 yr.	2.0 yr.	6 yr.	6.0 days	4 days (6 yr.)	8 days (2 yr.)
Shoe buckle.....	2	6.0 yr.	4.0 yr.	8 yr.			
False teeth.....	2	46.5 yr.	30.0 yr.	63 yr.			
Toy whistle.....	2	4.8 yr.	2.5 yr.	7 yr.	7.0 days	6 days (2.5 yr.)	8 days (7 yr.)
Campaign button.....	2	5.0 yr.	4.0 yr.	6 yr.	5.5 days	4 days (6 yr.)	7 days (4 yr.)
Phonograph needle.....	2	5.0 yr.	5.0 yr.	5 yr.			
Key.....	1	18.0 yr.	.....	.....	3.0 days		
Wood splinter (tooth pick).....	1	3.0 yr.	.....	.....			
Picture hanger.....	1	6.5 yr.	.....	.....	4.0 days		
Cup hook.....	1	2.0 yr.	.....	.....	5.0 days		
Jack stone.....	1	4.0 yr.	.....	.....	4.0 days		
Nonsharp steel.....	1	3.0 yr.	.....	.....			
Total.....	89	.....	.....	.....	5.1 days		

pointed at both ends required an average of seven days. Strangely enough, the open safety pins required an average of but four and six-tenths days for passage through the gastro-intestinal tract, a fact which is probably accounted for in that those pins which pass have the spring end foremost, while the two after-coming tips spread out in wedge fashion and may become entangled in the intestinal content and be carried along with it. While the various groups are not large enough from which to draw definite comparisons, it seems evident in evaluating the

the statement that the stomach and the duodenum are but rarely perforated, while the colon, particularly at the flexures, is the most frequent site of perforation.<sup>14</sup> In an effort to determine the accuracy of this statement, an extensive review of the reported cases was made. For reasons previously stated, cases of perforation of the esophagus, Meckel's diverticulum, appendix and rectum were excluded. With these exceptions, a total of 71 cases, including 9 seen at the Boston City Hospital and not previously reported, were collected and analyzed (table 3). Of the 71 cases, the stomach was found to have been perforated in 26, or 36.6 per cent; the duodenum in 10, or 13.9 per cent; the small intestine in 12, or 16.6 per cent; the cecum in 11, or 15.3 per cent, and the colon in 12, or 16.6 per cent. The perforation of the large intestine occurred in the sigmoid flexure in 6 cases.

In evaluating these figures it is necessary to stress again the point that it is impossible to arrive at accurate conclusions regarding the frequency with which various portions of the gastro-intestinal tract are perforated by an ingested foreign body. This is due to the inaccessibility of many of the reported cases and to the fact that a great many cases are not reported. However, from the foregoing figures it is fair to state that the stomach is probably perforated as frequently as is any portion of the gastro-intestinal tract. Perforation of the stomach by a foreign body carries with it the same implications as does perforation of a peptic ulcer, and surgical intervention should be no less prompt.

Foreign bodies perforate the gastro-intestinal tract by several methods: A pointed foreign body may be pushed through the stomach or intestinal wall by peristaltic activity. Such a perforation gives rise to symptoms of spreading peritonitis of acute onset. At operation no adhesions are found walling off the inflammatory process. In table 3 this has been designated as "acute perforation." In the series of 71 collected cases, 19 (26.4 per cent) were of this variety. A nonsharp as well as a sharp foreign body may penetrate the gastro-intestinal wall by means of ulceration due to pressure necrosis. Such a perforation becomes walled off with adhesions which limit the extent of the inflammatory reaction and give rise to symptoms of a subacute or a chronic nature. At times there is such an over-production of granulation tissue that large tumors are found which may readily be mistaken for neoplastic disease and in extreme cases may cause intestinal obstruction.

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14. (a) Bearse, Carl: Fishbones as a Cause of Intestinal Perforation, *New England J. Med.* **201**:885-886 (Oct. 31) 1929. (b) Ginzburg, Leon, and Beller, A. J.: The Clinical Manifestations of Non-Metallic Perforating Foreign Bodies, *Ann. Surg.* **86**:928-939 (Dec.) 1927. (c) Stone, Harvey B., and Owings, James C.: Perforation of the Stomach by a Fish Bone, *Am. J. Surg.* **25**:180-182 (July) 1934.

the right lower quadrant and which was decidedly different from the discomfort which she had previously noted. The pain became gradually and progressively worse until sixty hours before admission, when she was awakened from a sound sleep by a severe exacerbation of the same type of pain. It was aggravated by physical exertion, particularly by walking, and was noted to be more severe when she lay on her left than when she lay on her right side. The pain continued unabated until the patient's admission to the hospital and was accompanied by the vomiting of bitter, bile-tinged, watery material. At no time did she note blood in the vomitus or bloody, tarry or clay-colored stools. There were no chills, fever or diarrhea and no history of jaundice.

Physical examination revealed a rather obese woman who appeared to be in great pain. The temperature was 98.6 F., the pulse rate 72 and the respiratory rate 20. The blood pressure was 120 systolic and 70 diastolic. Except for the abdomen, the results of the physical examination were essentially negative. There was a well healed lower midline scar from the previous uterine suspension. Tenderness and mild involuntary muscle spasm were noted over the entire right upper quadrant, with the point of maximum tenderness in the midclavicular line, 2 inches (5 cm.) below the costal margin. No masses or viscerae were felt, and the results of the pelvic and rectal examinations were within normal limits. The red blood cell count was 4,250,000. The hemoglobin content 90 per cent and the white blood cell count 9,000. The urine was normal. The Hinton test was negative. The stools were negative for occult blood and parasites. Analysis of the gastric contents revealed no free acid after the alcohol meal or after the injection of histamine. The total acid content after the injection of histamine was 2 units.

Roentgenograms of the region of the gallbladder after the oral administration of the dye showed no filling of the gallbladder. A small vertical shadow opposite the interspace between the first and the second lumbar vertebrae (fig. 1) was noted, but its significance was not realized until the pictures were reviewed after the operative findings were known.

After three days of preoperative preparation, during which time there was no abatement of symptoms, operation was performed through a right upper rectus incision. When the peritoneal cavity was opened, a diffuse injection was noted on the anterior surface of the stomach and the transverse colon, with a small amount of peritoneal fluid. Further exploration revealed a minute perforation of the wall of the stomach on the anterior surface just proximal to the pyloric ring and about 1 cm. below the lesser curvature. Through this perforation protruded a fragment of chicken bone, 3.6 cm. in length (fig. 2). This was removed, and the defect was closed with a purse-string suture of chromic catgut. Exploration of the gallbladder revealed it to be small, thickened and bound down by numerous fibrous adhesions. No stones were present. Because the patient's condition was excellent and because she had a definite history of disease of the gallbladder of long standing, the adhesions were freed, and the gallbladder was removed from above downward. A cigaret drain was placed to Morrison's pouch, and the wound was closed in layers around the drain.

Postoperatively, the patient had an entirely uneventful convalescence. She was discharged home on the sixteenth postoperative day. One month after discharge she was entirely free from symptoms, and a meal of barium sulfate revealed no demonstrable pathologic process in the stomach or duodenum.

CASE 2.—Mrs. G. P., a white housewife aged 52, was admitted to the surgical service on Nov. 29, 1936, complaining of abdominal pain of seven hours' duration.



a piece of squash rind was found to have perforated the ileum. There was a surrounding localized peritonitis. The foreign body was removed, and the defect in the bowel was closed with a double tier of linen sutures. A drain was placed to the pouch of Douglas, and the wound was closed in layers.

The patient made an uneventful convalescence and was discharged home on the twenty-first postoperative day. When seen in the follow-up clinic one month later, she was entirely free from symptoms.

CASE 3.—R. C., a 7 month old boy, was admitted to the hospital on May 20, 1923. The mother stated that two days before admission the child had swallowed an open safety pin. He gagged a little at the time but had suffered no other symptoms. The results of the physical examination at the time of admission were negative. The abdomen was soft, symmetrical and tympanitic. There was no tenderness and no muscle spasm, and no masses were palpable. A roentgenogram of the abdomen showed an open safety pin, with the point directed downward, probably in the pyloric end of the stomach. The child was observed in the ward for eleven days, when a second roentgenogram showed no change in the position of the pin. Operation was performed the following day through a high midline incision. The open safety pin was located at the duodenojejunal flexure and was found to have perforated the wall of the bowel at this point. An incision was made in the intestinal wall, the pin was removed and the incision in the bowel was closed in the transverse diameter. The abdominal wall was closed in layers around a cigaret drain. Shortly after the operation, the patient began to fail. Despite vigorous supportive treatment, he died thirty-six hours postoperatively.

This case illustrates the necessity for the closest possible clinical and roentgen studies in cases of ingested foreign body. Undoubtedly the pin had perforated some time prior to operation, and had the operation been resorted to earlier the patient would no doubt have lived.

CASE 4.—J. H., an 8 year old school boy, was admitted to the hospital on April 30, 1923, complaining of pain in the right side of the abdomen of twenty-four hours' duration. The pain had been of rather sudden onset and was constant; it was worse in the right lower quadrant. The patient was given castor oil at the time of the onset and had had watery diarrhea since. There was no nausea or vomiting. Physical examination revealed a well developed and well nourished boy of 8 who appeared to be acutely ill. The temperature was 100 F., the pulse rate 100 and the white blood cell count 12,000. There was marked tenderness without muscle spasm in the right lower quadrant of the abdomen, and a tender mass was palpable just above Poupart's ligament on the right side. Soon after the patient's admission to the hospital the abdomen was explored through a right lower rectus incision. The appendix was normal and was removed in the usual fashion. Further exploration revealed a deeply injected piece of small bowel through which a wooden splinter had perforated. The surrounding intestine and mesentery were covered with fibrin, but there was no free pus. The foreign body was removed, and the opening in the bowel was closed with a purse-string suture. The abdominal wall was closed around a drain placed to the region of the perforation. The patient made an entirely uneventful convalescence and was discharged home on the fourteenth postoperative day.

CASE 5.—G. L. F., a 34 year old schoolteacher, was admitted to the hospital on Aug. 19, 1936, complaining of being weak, run down and overworked for the past

on the following day the pain had returned in all of its severity and continued to become progressively worse until the patient's admission to the hospital at noon.

Physical examination revealed a well developed and well nourished man who was in great pain. There was marked tenderness in the epigastrium with involuntary muscle spasm throughout the upper portion of the abdomen. The tenderness was somewhat more marked just to the right of the midline. Rectal examination gave negative results. The white cell count was 20,000 per cubic millimeter of blood. The urine was normal, and fluoroscopy of the abdomen showed no evidence of pneumoperitoneum.

Operation was performed through a right upper rectus incision soon after the patient's admission. There was a moderate amount of clear serous fluid in the peritoneal cavity. A piece of wood,  $1\frac{1}{2}$  inches long, was found near the stomach. The omentum was adherent to the anterior wall of the pylorus and, more particularly, to the first portion of the duodenum, and the point of perforation could not be found, undoubtedly being under the adherent omentum. A drain was placed to the region of the pylorus, and the wound was closed in layers around the drain.

The postoperative convalescence was complicated by paralytic ileus secondary to a subfascial abscess of the wound.

During his convalescence the patient identified the small sliver of wood as being a part of the seasoning used in the preparation of the spaghetti eaten six hours before the onset of his acute symptoms. In view of the completeness with which the perforation was walled off, it seems likely that penetration of the duodenum had been going on for some time, causing the recurrent bouts of indigestion, and that perforation finally occurred twenty-four hours before admission into a field which was already well walled off by omentum. The vegetable seasoning (dried thyme) was used frequently in the patient's food, and the bit causing the perforation may have been swallowed some time before.

The patient was seen twenty months after his discharge from the hospital, at which time he was enjoying excellent health. Appetite and digestion were normal, and he had gained 20 pounds (9.1 Kg.) since the operation. Serial roentgenograms of the gastro-intestinal tract showed no evidence of a pathologic process in the stomach or duodenum.

Cases 1 and 7 illustrate the complete healing of the stomach and duodenum, respectively, after perforation of their walls by foreign bodies. Roentgenograms of the gastro-intestinal tract in each case failed to demonstrate scarring or any other pathologic process.

CASE 8.—W. B., a 15 year old school boy, was admitted to the hospital on Jan. 24, complaining of pain in the left lower abdominal quadrant of one month's duration. One month before admission he had accidentally swallowed a common pin. Two days later he began to suffer with the pain, which persisted until the time of entry. Physical examination revealed a well developed and well nourished boy in no great distress. The temperature was 98.8 F. and the pulse rate 80. The abdomen was soft and symmetrical throughout. There was slight tenderness throughout the entire left side of the abdomen, which was not well localized. There was no muscle spasm, and no masses were felt.

Roentgen examination revealed a long pin in the descending colon, which could be seen piercing the wall of the bowel.

Twenty-four hours after admission the patient was operated on through a lower left rectus incision. The pin was found protruding through the wall of the descend-

perforation occurred. The group in which perforation of the small bowel occurred commanded a mortality of 20 per cent, while, strangely enough, there were no deaths in 9 cases in which the large bowel (exclusive of the cecum) had been perforated.

Of the many thousands of cases of appendicitis seen at the Boston City Hospital, there is no record of a case in which the appendix had been perforated by a foreign body. This is rather remarkable in view of the not infrequent reports seen in the older surgical literature.<sup>1</sup> Only 7 cases of perforation of Meckel's diverticulum have been reported in the literature.<sup>15</sup> No such case has been seen at the Boston City Hospital.

TABLE 4.—*Result of Operation for Perforation in Cases in Which Result is Known*

Part of Gastro-Intestinal Tract	Acute Perforation, No. of Cases	Chronic Perforation, No. of Cases	Abscess Formation, No. of Cases	Not Stated, No. of Cases	Total Cases	Mortality for All Types of Perforation, %
Stomach.....	..	..	..	..	..	23.0
Recovery.....	3	8	7	..	18	
Death.....	1	3	3	..	7	
Duodenum.....	..	..	..	..	..	0.0
Recovery.....	2	2	..	..	4	
Death.....	0	0	..	..	0	
Small bowel.....	..	..	..	..	..	20.0
Recovery.....	5	2	1	..	8	
Death.....	1	0	1	..	2	
Cecum.....	..	..	..	..	..	22.2
Recovery.....	1	1	4	1	7	
Death.....	2	0	0	0	2	
Large bowel (exclusive of cecum) ..	..	..	..	..	..	0.0
Recovery.....	2	2	5	..	9	
Death.....	0	0	0	..	0	
Average mortality.....					57	14.0

Wölfler and Lieblein<sup>10</sup> found 35 cases in which foreign bodies had been involved in the contents of various types of hernia. There was abscess formation in 7 of these cases. Ginzburg and Beller<sup>14b</sup> have observed 2 such cases. Reports of this type of case are comparatively rare, and none have been seen at the Boston City Hospital.

It is interesting to speculate as to the possible relationship of a foreign body in the gastro-intestinal tract and a pyogenic abscess of the psoas muscle. James<sup>10</sup> reported the case of a child of 2½ years who was seen because of pain in the right thigh and flexion deformity of

15. Eitel, G. D.: Ingested Foreign Bodies in the Gastro-Intestinal Tract Requiring Surgical Removal, *Minnesota Med.* 18:52-59 (June) 1935.

16. James, T. G. I.: Psoas Spasm Caused by a Foreign Body, *Brit. J. Surg.* 22:622-623 (Jan.) 1935.

reported a case of fatal gastric hemorrhage from an ingested fish bone which had perforated the posterior wall of the stomach. Benda<sup>18</sup> found a fish bone in the superior mesenteric vein.

*Foreign Bodies too Large to Pass Through the Gastro-Intestinal Tract.*—Of the ingested foreign bodies which are too large to pass through the gastro-intestinal tract, the open safety pin presents a problem unto itself. The pin is usually swallowed by an infant or a young child, and often the activating motive behind the act is the poor example set by the mother in putting pins in the mouth while dressing the child. As stated previously, an open safety pin which passes always has the spring foremost. The pin which becomes impacted always has the open wedge, formed by the point and the head, foremost. A pin in such a position usually becomes impacted at the outlet of the stomach and in such a position frequently must be removed surgically. A case in point is the following:

CASE 11.—A. R., a 9 month old girl, was admitted to the hospital on July 9, 1931. The mother stated that thirty hours before admission the child had swallowed an open safety pin. She gagged slightly at the time but had been perfectly well since and was taking food and fluids normally. Physical examination gave negative results. The day of admission, while in the ward, the child vomited a small quantity of bright red blood. A roentgenogram of the abdomen on that day showed a large safety pin, open and with point downward, lodged in the pylorus. A second roentgenogram the following day showed no change in the position of the pin.

Operation was performed the day after the child's admission through a left upper rectus incision. The safety pin was palpated through the wall of the stomach. A  $\frac{1}{2}$  inch (1.3 cm.) incision was made in the anterior wall of the stomach, and the pin was removed. The wound in the gastric wall was closed, and the abdomen was closed in layers without drainage. Convalescence was entirely uneventful, and the patient was discharged from the hospital on the eleventh post-operative day.

There are several other methods of dealing with an open safety pin and other similar small foreign bodies in the stomach and the first portion of the duodenum. Five cases are reported<sup>19</sup> in which at lapa-

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18. Benda, C.: Fremdkörper in der Vena meseraica superior, Berl. klin. Wchnschr. **47**:2110, 1910; cited by Bearse, C.: Fishbones as a Cause of Intestinal Perforation, New England J. Med. **201**:885-886 (Oct. 31) 1929.

19. (a) Greeley, Paul W.: Removal of Slender Foreign Bodies from the Stomach and Duodenum Without Gastrotomy or Duodenotomy, J. A. M. A. **101**: 119 (July 8) 1933. (b) Huff, W. B.: Removal of a Safety Pin from Stomach Without Gastrotomy, *ibid.* **94**:1655-1656 (May 24) 1930. (c) Monteith, W. B. R.: Removal of Foreign Body from Stomach of Infant, Brit. M. J. **1**:259 (Feb. 18) 1928. (d) Otten, Harry: Open Safety Pin in Stomach of Two Months Old Baby, J. A. M. A. **100**:736 (March 11) 1933. (e) Raymond, Sidney W.: Foreign Body in Duodenum: Report of Case and Method of Removal, *ibid.* **100**:337 (Feb. 4) 1933.

CASE 14.—J. T., a 2 year old girl, was admitted to the hospital on Sept. 3, 1920, with a history of having swallowed a "stickpin," 3 inches (7.6 cm.) in length, twenty-four hours previously. There had been no subjective symptoms, and physical examination gave negative results. Fluoroscopic examination revealed the pin in the right upper quadrant. After six days' observation in the ward, further roentgen examination showed that the pin had not changed position. Operation was performed the following day through a right upper rectus incision. The pin was easily felt in the second portion of the duodenum. A small incision was made in the wall of the duodenum, and the pin was delivered through it. The incision in the intestine was closed with a double tier of catgut sutures, and the abdominal wall was closed without drainage.

Convalescence was complicated by scarlet fever, from which the child recovered after treatment in the contagion service. Slight superficial sepsis of the wound was easily controlled.

In dealing with an impacted foreign body one must keep constantly in mind the fact that there is a tendency for such an object to pass naturally, occasionally after long periods of remaining in the same location. It is necessary in all cases to make a roentgenogram of the abdomen immediately before operation to be certain of the location of the foreign body. By so doing, much operative trauma will be avoided, and an occasional patient will be spared the necessity of operation, as would have been the case in the following instance:

CASE 15.—J. G., an 11 year old school boy, was admitted to the hospital on Sept. 23, 1929, with a history of having swallowed a nail three weeks before. He was seen in the outpatient department the day of the accident, and roentgen examination at this time showed the nail to be in the stomach. One day later the nail was seen on roentgen examination to be lodged in the second portion of the duodenum. Frequent roentgenograms showed no progress of the foreign body, and the child was finally admitted to the hospital for operation, having suffered no untoward effects in the interval. Physical examination at the time of admission gave negative results. Further roentgenograms at the time of admission to the hospital and on the succeeding two days showed no progress of the foreign body. Operation was performed through a right rectus incision on the fourth day of hospitalization. The stomach and duodenum were carefully palpated, but no foreign body was felt. The ligament of Treitz was divided, and the entire duodenum was searched without success. Further exploration of the intestinal tract revealed the nail in the lower portion of the ileum, from which it was removed through a small incision in the wall of the bowel. Postoperative convalescence was uneventful.

*Foreign Bodies Causing Obstruction to the Gastro-Intestinal Tract.*  
—A foreign body which passes the esophagus ordinarily does not cause obstruction to the gastro-intestinal tract. Such an obstruction is usually due to multiple foreign bodies or to one of the several classes of bezoars. These usually cause symptoms of intermittent pyloric obstruction, with or without the presence of a palpable epigastric mass. In the case of a metal foreign body, the diagnosis is readily made by a simple roentgen-

ination of the abdomen should be done with great care in order to form a basis for comparison with subsequent examinations. Should abdominal tenderness develop in a patient who has swallowed a foreign body, particularly if the foreign body is pointed at one or both ends, laparotomy should be performed at once.

In the case of a radiopaque foreign body roentgen examination is of the greatest importance and should include not only anteroposterior but lateral views as well. In this way it is usually possible to determine the location of the foreign body in the gastro-intestinal tube. In this respect it is interesting to note the ingenuity displayed by clinicians before the days of the x-ray. Cant<sup>24</sup> reported the case of a woman who was said to have swallowed a razor. The patient was given 20 minims (1.2 cc.) of dilute hydrochloric acid. After one hour the contents of the stomach were aspirated, and the washings were filtered, evaporated and redissolved. The presence of iron in large quantities was demonstrated by means of the prussian blue test.

The preoperative diagnosis of acute or chronic perforation of the gastro-intestinal tract by a foreign body will seldom be made in the absence of a definite history of ingestion of a foreign body. It should be suspected in cases of peritonitis in which the etiology is atypical. When the suspected pathologic process is not found at operation, it is important to explore the infected region with perforation by a foreign body in mind, so that the etiologic factors may be adequately dealt with.

*Treatment.*—Treatment for an ingested foreign body in the absence of perforation should always be conservative, until it is definitely shown that the foreign body will not pass naturally or until it is evident that there is, or is about to be, perforation. Careful daily examinations of the abdomen should be made. With the development of abdominal tenderness, laparotomy should be performed without delay. Daily roentgenograms of the abdomen, both anteroposterior and lateral, should be made so that the progress of the foreign body through the gastro-intestinal tract can be watched. It has been shown previously that foreign bodies which pass the gastro-intestinal tract usually do so within seven days from the time of ingestion. Surgical intervention should therefore be considered seriously in the case in which the foreign body remains in one place in relation to the viscerae (not necessarily in relation to the bony landmarks) for seven days or more. It is also important that stools be strained to confirm the passage of the foreign body through the gastro-intestinal tract.

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24. Cant, W. J.: Case of Swallowing a Razor; Gastrotomy; Death, *Lancet* 1:20-21, 1893.

Muthis* (1602), cited by Friedenwald and Rosenthal <sup>4</sup>	Knife 21 cm. long	Stomach (pylorus)	Chronic penetration (?)	Present in stomach 51 days	.....	Application of plasters to abdomen; penetration of pylorus by knife; removal of knife	Recovery
Wessner (1602), cited by Friedenwald and Rosenthal <sup>4</sup>	Knife	Stomach	Abscess formation	Abscess of abdominal wall 7 mo. after ingestion of foreign body	.....	Drainage of abscess; knife presented in wound; knife removed	Recovery
Huebner (1720), cited by Friedenwald and Rosenthal <sup>4</sup>	Knife 16.5 cm. long	Stomach	Abscess formation	Acute abdominal pain 3 days after swallowing foreign body	.....	Drainage of abscess of left side of hypochondrium; knife presented in wound on eleventh day; removal of knife	Recovery
Frisne (1786), cited by Friedenwald and Rosenthal <sup>4</sup>	Knife 4.5 cm. long	Stomach	Chronic penetration (?)	Present in stomach 11 days	.....	Epigastric incision; penetration of wall of stomach by knife; removal of knife	Recovery
Edell (1836), cited by Friedenwald and Rosenthal <sup>4</sup>	Brass fork and 4 pronged fork without handle 10 cm. long	Stomach	Abscess formation	Present 2½ yr.; abscess of right side of hypochondrium after 15 mo.; drainage of abscess for 11 mo. later; removal of foreign bodies	.....	Drainage of abscess and removal of foreign bodies	Recovery
Holbeck* (1853), cited by Friedenwald and Rosenthal <sup>4</sup>	Fork 21 cm. long	Stomach	Abscess formation	Nausea, anorexia, vomiting; abscess of abdominal wall	.....	Drainage of abscess; foreign bodies extracted	Died 3 mo. later of caries of sternum and ribs
Ozerny (1895), cited by Friedenwald and Rosenthal <sup>4</sup>	Needle	Stomach	Acute perforation	Abdominal pain for 8 days; epigastric tenderness	.....	Induration at point of perforation; no adhesions	Recovery
Hashimoto (1880), cited by Friedenwald and Rosenthal <sup>4</sup>	Tooth brush	Stomach (anterior wall)	Abscess formation	Object in stomach 7 days	.....	Perforation of anterior wall of stomach; point of perforation excised and resutured after removal of foreign body; peritonitis present	Died of peritonitis
Hullwell (1899), cited by Friedenwald and Rosenthal <sup>4</sup>	Hat pin	Stomach (posterior wall)	Acute perforation	Pain in left iliac fossa and tenderness over descending colon	.....	Colon normal; needle in stomach with point embedded in posterior wall; point pushed through stomach and omentum and lead passed by rectum	Recovery
Ingh (1902), cited by Friedenwald and Rosenthal <sup>4</sup>	Nails, pins, needles and buttonhook (12 articles)	Stomach	Chronic penetration (?)	Abdominal pain and distress	.....	Perforation of stomach by pin; stomach opened and emptied; foreign bodies removed from ileum	Recovery
Galtner, F. H.; M. Clin. North America 10: 1185-1197, 1933	Prune seed	Ileum	Acute perforation	Recurrent pain in lower part of abdomen for 1 mo.; sudden severe pain in lower part of abdomen	Acute appendicitis	Prune seed free in abdominal cavity; resection of 30 cm. of ileum and side to side anastomosis	Recovery

Common pin	Descending colon	Chronic perforation	Pain in left lower quadrant for 1 mo.; pin swallowed 2 days before onset of symptoms; tender throughout left side of abdomen	Correct (roentgenographic)	Extraction of pin; closure of defect in colon and of defect where pin had perforated a loop of ileum; drainage	Recovery
Open safety pin	Duodeno-jejunal flexure	Acute perforation	7 mo. infant; pin swallowed 12 days before operation; no progress by roentgen examination	Correct (roentgenographic)	Extraction; closure of defect; drainage	Died
Wood splinter	Small intestine	Acute perforation	Pain in right lower quadrant for 24 hr.; tenderness in right lower quadrant	Acute appendicitis	Closure of defect after removal of foreign body; incidental appendectomy; drainage	Recovery
Pieces of bed spring	Cecum	Acute perforation	Abdominal pain and tenderness	Correct (roentgenographic)	Perforation of cecum; removal of 6 pieces of bed spring from cecum; 4 from sigmoid flexure with lead pencil and 4 matches; no perforation of sigmoid flexure	Died
Wood splinter	Transverse colon	Acute perforation	Pain in right lower quadrant for 7 days; tenderness and spasm in right lower quadrant	Acute appendicitis	Incidental appendectomy; closure of defect after removal of foreign body	Recovery
Squash rind	Ileum	Acute perforation	Abdominal pain for 7 hr.	Acute appendicitis	Foreign body removed; defect closed; drainage	Recovery
Chicken bone	Sigmoid flexure (diverticulum)	Chronic perforation	Vesicoecolic fistula	.....	Four stage operation	Recovery
Needle	Duodenum (posterior wall of first portion)	Acute perforation	Pain in upper part of right thigh and flexion deformity of hip	Correct	Needle penetrated into psoas muscle; removal; closure of defect	Recovery
Lead pencil	Stomach	Chronic penetration	Intense abdominal pain with spasm; white cell count 25,000	.....	Removal of pencil; closure of defect; drainage	Recovery
Wire 2 inches long	Stomach (pyloric end)	Chronic penetration	Pain for 4 days in right side of abdomen	Acute appendicitis	Wire perforated into large omental mass; removal of wire; drainage; died of peritonitis	Died
Common pin	Cecum (near base of appendix)	Acute perforation	Abdominal pain for 1 wk. with signs of general peritonitis	Acute appendicitis	Died 1 hr. after operation	Died
Tooth pick	Sigmoid flexure (diverticulum)	Abscess formation	.....	.....	Drainage of abscess	Recovery
Campalgn button	Sigmoid flexure (malignancy of)	Abscess formation	.....	.....	Drainage of abscess	Recovery

Herbst, R. H., and Miller, E. M.:  
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1930

James<sup>10</sup>.....

Little, Y. A.: J. A. M. A. 62: 929-930  
(March 21) 1914

Lupton, W. J. E.: Lancet 2: 1179-  
1180 (Dec. 3) 1927

Macewen, J. A. G.: Lancet 2: 785,  
1919

Maxeiner, S. R., in discussion on  
Bile,<sup>12</sup> p. 581



	Open safety pin	Cecum	Abscess formation	Pain in right upper quadrant	.....	Local peritonitis present	
Sivertsen, L., in discussion on Eitel <sup>15</sup>	Bits of screen wire	Small bowel	Acute perforation	.....	.....	Resection	Recovery
Stone and Owings <sup>14c</sup>	Fish bone	Stomach	Chronic penetration	Epigastric pain for 6 mo.; palpable epigastric mass	.....	Resection of portion of stomach together with adherent omentum; fish bone found in sectioning specimen	Recovery
Tuft, L.: M. J. & Rec. 119: 30, 1924	500 straight pins	Stomach	Chronic penetration	Pins swallowed with suicidal intent 7 wk. before operation	.....	Large perforation of stomach with local peritonitis; pins removed	Died
Vestal, P. W.: New England J. Med. 203: 1192-1200, 1930	Tooth pick	Cecum	Abscess formation	Three days of symptoms simulating acute appendicitis	Acute appendicitis	Perforation of antero-lateral aspect of cecum opposite ileocecal valve; removal of foreign body; closure of defect; drainage	Recovery
Wallace, J. T.: Am. J. Surg. 19: 453-455, 1933	Open safety pin	Duodenum, 2d portion	Chronic penetration	Pin remained stationary for 7 days	.....	Point of pin just under serosa, covered by adherent omentum; removal of pin; closure of defect	Recovery
Wheeler, P. H.: New England J. Med. 214: 830-832, 1936	Multiple tacks, staples, etc.	Stomach, lesser curvature	Chronic penetration	Vomiting of blood and coffee-ground material for several months	Correct (roentgenographic)	Excision of perforated ulcer caused by foreign bodies; removal of foreign bodies	Recovery
Wöfler and Lieblein <sup>16</sup>							
Schwabe.....	.....	Stomach					
Soyka-Chlari.....	.....	Duodenum					
Winge.....	.....	Ileum portion of terminal					
von Kranzle.....	.....	Duodenum					
Dienerbrock.....	.....	Small intestine	Acute perforation				
Dehnor.....	Wire	Ileum	Abscess formation				
Menzel.....	Lint	Transverse colon	Abscess formation				
Brevitt.....	Penell	Ascending colon	Chronic penetration (?)				
Gummel.....	Nail	Stomach	Acute perforation (?)				

## SUMMARY AND CONCLUSIONS

1. Foreign bodies swallowed by infants and young children are usually the result of carelessness on the part of parents. Dentures covering a large part of the sensitive area of the mouth are frequently responsible for an adult unwittingly swallowing a foreign body.

2. An ingested foreign body that passes per vias naturales usually does so within seven days, regardless of the age of the patient or the type of the foreign body.

3. An ingested foreign body that perforates the gastro-intestinal tract may do so at any point along the tract. Statistically, the stomach seems to be perforated about twice as frequently as is any other portion.

4. Acute perforation of the gastro-intestinal tract by an ingested foreign body is most likely to occur in the small intestine or cecum. Chronic perforation and abscess formation are more likely to occur in the stomach and colon. Cases seen at the Boston City Hospital are presented illustrating the various types of perforation.

5. It is suggested that a foreign body perforating the gastro-intestinal tract and becoming embedded in the substance of the psoas muscle may occasionally be responsible for pyogenic abscess of the muscle.

6. Hemorrhage from the gastro-intestinal tract caused by an ingested foreign body is unusual. One such case seen at the Boston City Hospital is presented.

7. The problem of the ingested open safety pin is discussed.

8. The curves of the duodenum are a frequent site of impaction of elongated foreign bodies. Surgical intervention for an impacted foreign body should always be immediately preceded by roentgen examination to determine whether or not the foreign body has changed position in the twenty-four hours preceding operation.

9. A discussion of the indications for, and the essential details of, the conservative and surgical treatment for an ingested foreign body is given.

Germany and Switzerland. Wegelin,<sup>3</sup> Hesselberg,<sup>4</sup> Zelinska,<sup>5</sup> Kloeppel,<sup>6</sup> Isenschmid,<sup>7</sup> Sanderson,<sup>8</sup> Schaer<sup>9</sup> and Clerc<sup>10</sup> are the principal ones from whom these data can be obtained.

Alexander Hellwig<sup>11</sup> seems to have obtained a clear idea of the variabilities in the structure of the thyroid gland in North America. He pointed out that the acini and the incidence of nodules may vary in size and percentage, respectively, depending on age and locality.

In a previous study of the life cycle of the thyroid gland from Minnesota it has been shown that there may be numerous variations in the gross and the histologic structure of the normal gland.

#### MATERIAL AND METHOD OF INVESTIGATION

This paper deals with the same material as that which was used in a previous paper.<sup>12</sup> Five hundred thyroid glands were examined grossly and histologically. These glands were taken from persons who died of diseases in which the thyroid gland played no part and who were not accredited with a goiter during their routine physical examination made at the time of their admission to the hospital. Large glands or glands which were found to contain nodules were not excluded from the series unless the presence of a "goiter" had been noted on routine physical examination.

All glands were serially sectioned for gross examination, and histologic sections were made from representative areas. The percentage incidence of nodules was determined. The acini were measured with a micrometer, and the size and shape

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3. Wegelin, C.: Die Schilddrüse, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 8.

4. Hesselberg, Cora: Die menschliche Schilddrüse in der foetalen Periode und in den ersten sechs Lebensmonaten, *Frankfurt. Ztschr. f. Path.* **5**:322-350, 1910.

5. Zelinska, Marie: Beitrag zur Kenntnis der normalen und strumösen Schilddrüse des Menschen und des Hundes, *Virchows Arch. f. path. Anat.* **136**: 170-194, 1894.

6. Kloeppel, Franz C.: Vergleichende Untersuchungen über Gebirgsland- und Tieflandschilddrüsen, *Beitr. z. path. Anat. u. z. allg. Path.* **49**:579-593, 1910.

7. Isenschmid, Robert: Zur Kenntnis der menschlichen Schilddrüse im Kindesalter, *Frankfurt. Ztschr. f. Path.* **5**:205-254, 1910.

8. Sanderson, Elizabeth: Die Schilddrüsen vom 15-25 Lebensjahr, aus der Norddeutschen Ebene und Küstengegend sowie aus Bern, *Frankfurt. Ztschr. f. Path.* **6**:312-334, 1911.

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10. Clerc, Edward: Die Schilddrüse im hohen Alter. Vom 50. Lebensjahr an, aus der norddeutschen Ebene und Küstengegend sowie aus Bern, *Frankfurt. Ztschr. f. Path.* **10**:1-19, 1922.

11. Hellwig, C. Alexander: *Geographic Pathology of Goiter*, Surg., Gynec. & Obst. **55**:35-44, 1932; Die Lebenskurve der nordamerikanischen Schilddrüse, *Endokrinologie* **5**:323-336, 1933.

12. Rice, Carl O.: Life Cycle of the Thyroid Gland in Minnesota, *West. J. Surg.* **39**:925-940, 1931.

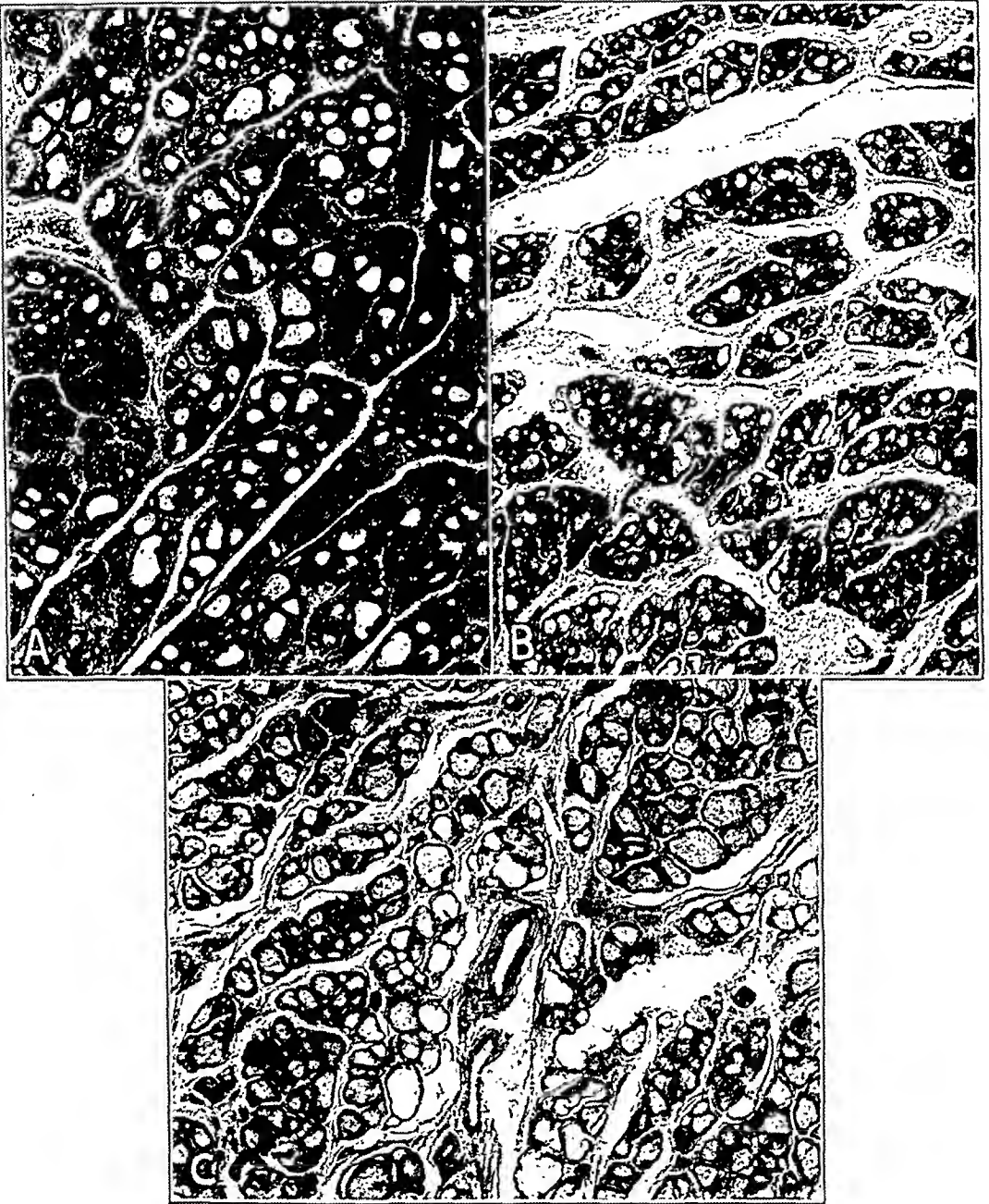


Fig. 2.—*A*, a section from the thyroid gland of a stillborn infant. The gland weighed 1.7 Gm., and the acini measured 84 microns in diameter. The interlobular septums are distinct, there is no colloid and there are many interacinar epithelial cells. Magnification,  $\times 174$ . (All photomicrographs are of the same magnification, except figure 4*C*, which was erroneously photographed at a magnification of  $250\times$ .) *B*, a section from the thyroid gland of a 3 month old infant. The gland weighed 2.3 Gm., and the acini measured 62 microns in diameter. There is an abundance of interlobular fibrous tissue, the colloid is beginning to appear and the interacinar epithelial cells are less abundant than in *A*. *C*, a section from the thyroid gland of a 6 month old child. The gland weighed 2.2 Gm., and the acini measured 134 microns in diameter. The interlobular septums are still distinct, the colloid occupies most of the acini and there is little interacinar epithelium.

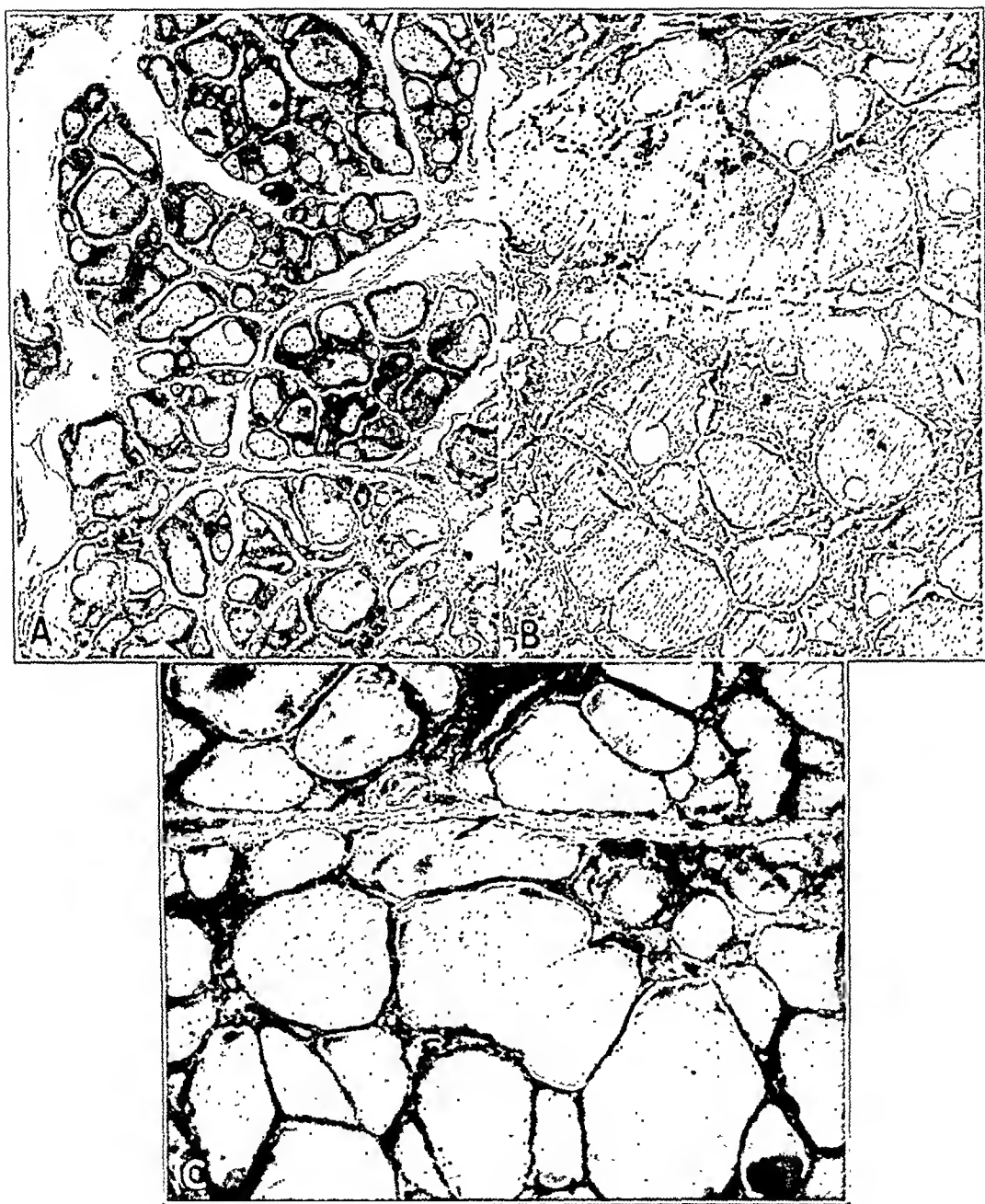


Fig. 4.—*A*, a section from the thyroid gland of a 7 year old child. The gland weighed 5.1 Gm., and the acini measured 201 microns in diameter. The interlobular septums are still evident, and the acini are filled with colloid. *B*, a section from the thyroid gland of a patient aged 15 years. The gland weighed 13.5 Gm., and the acini measured 336 microns in diameter. The interlobular septums are indistinct, the colloid is dense and the acinar epithelium is low cuboidal. *C*, a section from the thyroid gland of a patient aged 22. The acini measured 475 microns in diameter. The thyroid gland reaches its largest size in early adult life.

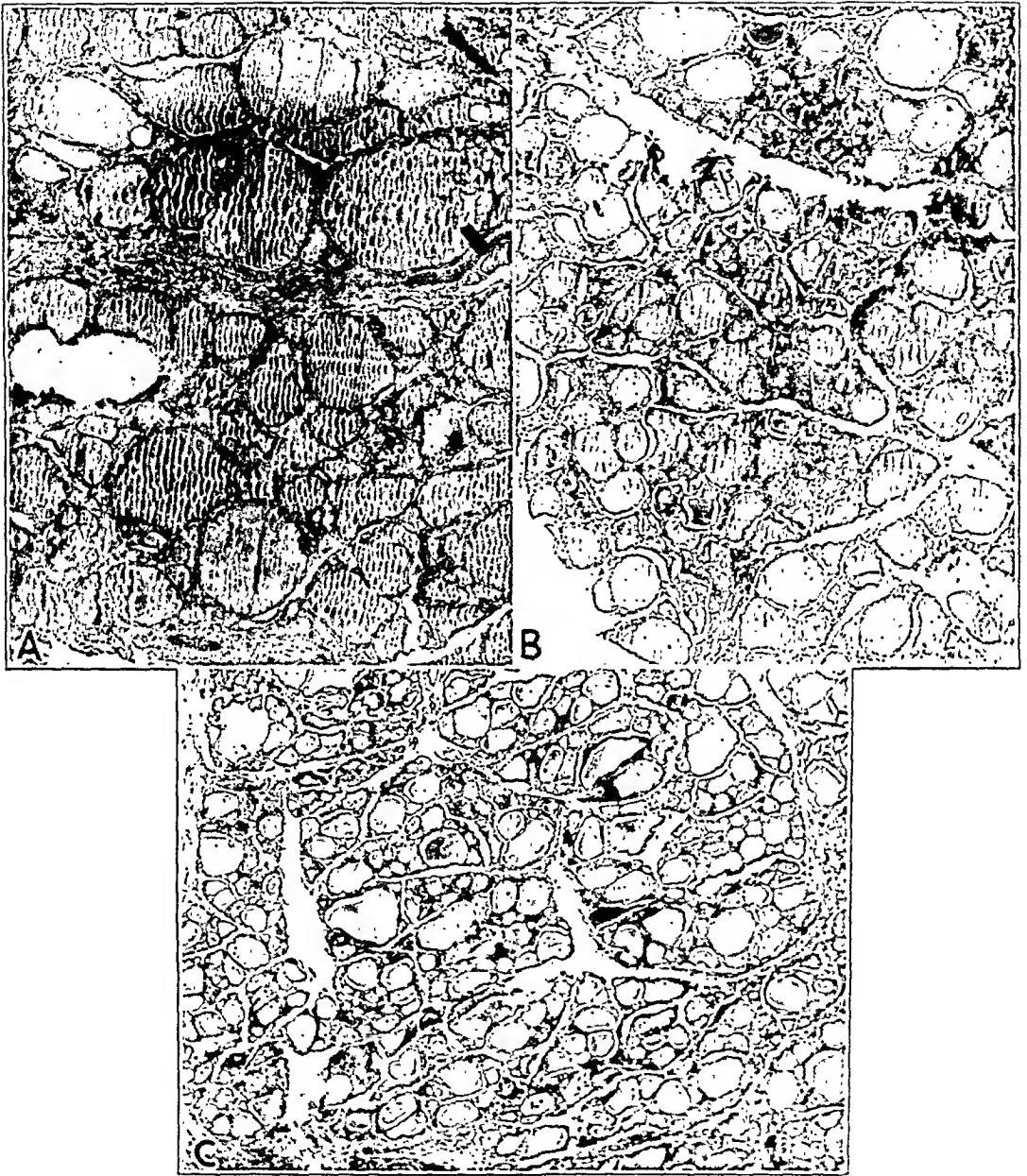


Fig. 5.—*A*, a section from the thyroid gland of an adult aged 39. The gland weighed 39 Gm., and the acini measured 336 microns in diameter. The acini are well filled with colloid and are beginning to show less uniformity in size than those from younger persons. As the person grows older, the lack of uniformity becomes more evident, as indicated in figures 5 *B* and *C* and 6 *A* and *B*. The acinar epithelium is cuboidal and flat. *B*, a section from the thyroid gland of an adult aged 45. The gland weighed 27.2 Gm., and the acini measured 252 microns in diameter. The interacinar epithelium is more abundant than in *A*. *C*, a section from the thyroid gland of an adult aged 55. The gland weighed 14.9 Gm., and the acini measured 168 microns in diameter. The interlobular septums are becoming more evident.

## NODULES

There is still another change which occurs in a certain percentage of otherwise normal thyroid glands which often leads to confusion in the interpretation of diseases of the thyroid gland, that is, the presence of nodules.

A nodule is a localized area of new growth having its origin within a lobule. The consensus at this time is in accordance with the views of Hitzig and Michaud, who expressed the belief that these nodules had their origin as the result of development from normal thyroid tissue by metaplasia of the epithelial cells within a localized area, the normal thyroid tissue being displaced so as to form a complete secondary lobule or nodule.

Nodules may be classified histologically into four groups: colloid, parenchymatous (fetal), mixed and degenerate. The colloid nodule is one in which the acini are large and filled with colloid (fig. 7 C). The parenchymatous nodule is one in which there are small acini, giving the appearance of the fetal thyroid, or solid packs of epithelial cells. The mixed nodule has been designated as one in which the histologic structure of both the parenchymatous and the colloid nodule is present. The degenerate nodule is one in which there are degenerative changes, such as hemorrhage, cystic formation, calcification and hyalinization. These changes may occur in any of the other types of nodules.

The histologic structure of these nodules may be extremely variable. There may be all sizes and shapes of acini; the epithelial cells may be small, and the interacinar epithelium may be abundant or sparse. Occasional bands of fibrous or hyaline stroma may be seen, but no true interlobular stroma can be identified within a nodule. No definite correlation can be made between the histologic structure within the nodule and the clinical symptoms of the patient.

The thyroid tissue adjacent to the nodule may be compressed and thereby altered (fig. 7 C), but more remote sections have failed to disclose any pathologic changes which might have been attributed to the nodule. The presence of a nodule in a gland does not alter the histologic structure of the remaining portion of that gland, except as its presence may alter the adjacent tissue. Likewise, the presence of a toxic adenoma has failed to show evidence of having altered the remaining parenchyma of the thyroid.

Nodules are rarely if ever observed in the thyroid gland in infancy. They have their inception at puberty or later. At puberty 2 or 3 per cent of persons have nodules within their thyroid glands. This incidence increases rapidly with the advance in age. Roughly, this incidence in Minnesota may be represented by the same figure as the age of the

group of persons under consideration; for example, approximately 30 per cent of persons at 30 years of age have nodules within their glands (fig. 8). In old age most of the glands can be found to contain nodules within their structure.

It is not intended to infer that all these nodules are clinically palpable but that they are found macroscopically when gross serial sections are made through glands which have been removed at autopsy from patients dying from other causes than from diseases of the thyroid gland.

The development of these nodules has been attributed by some authors to the physiologic strains encountered during a life time. In favor of this opinion, puberty and the child-bearing period have been cited as examples of physiologic stress. In corroborating these assumptions with the demonstrable facts, it is found that the incidence of nodules at puberty in both males and females makes an abrupt rise over that of the prepuberty period. A similar increase in the incidence is not observed in the male at the period corresponding to the child-bearing period for the female (fig. 8).

At 34 years of age, the average age of patients with exophthalmic goiter, approximately 34 per cent of the normal glands contain nodules. Therefore, it should not be unreasonable to suppose that 34 per cent of the glands from patients suffering from exophthalmic goiter will contain nodules within their structure. This fact was clearly demonstrated in a previous paper.<sup>13</sup> The presence of a nodule, therefore, should not confuse the clinician to the extent of stimulating him to call every exophthalmic goiter in which a nodule can be demonstrated a toxic adenoma. This has been investigated in another way on the assumption that exophthalmos is a sign found only in the patient whose gland shows diffuse hypertrophy and hyperplasia.

Among 121 goiters at the Minnesota General Hospital which were diagnosed clinically as toxic adenoma, there were 10 from patients who showed exophthalmos on physical examination. The study of these 10 patients who presented clinical signs and symptoms characteristic of exophthalmic goiter, including exophthalmos, convinced me that the growth was wrongly diagnosed as toxic adenoma because of the presence of palpable nodules. A diagnosis of exophthalmic goiter should have been made on the basis of the exophthalmos. All these glands were reexamined. In each the parenchymatous portion of the gland, i. e., that portion of the gland outside the nodule, showed hypertrophy and hyperplasia in a more or less marked degree (fig. 7 *A* and *B*). This finding was significantly absent in those cases of toxic adenoma in which the

13. Rice, Carl O.: Incidence of Nodules in the Thyroid, *Arch. Surg.* **24**:505-515 (March) 1932; Exophthalmic Goiter Versus Toxic Adenoma, *Minnesota Med.* **17**:361-364, 1934.



patients did not have exophthalmos. In these, the histologic structure of the parenchymatous portion of the gland contained normal acini (fig. 7 C).

Most writers will agree that the histologic changes in an exophthalmic goiter consist of diffuse parenchymatous hypertrophy and hyperplasia, which are altered only by the severity of the disease and the administration of iodine. The histologic changes in a toxic adenoma have not been as uniformly decided. Some writers have observed hypertrophy and hyperplasia within the nodule with no changes of the parenchymatous portion of the gland, whereas others have observed hypertrophy and hyperplasia both inside and outside the nodules, and thereby have been led to believe that toxic adenoma and exophthalmic goiter present essentially the same pathologic changes. I am of the opinion that the latter picture is that of exophthalmic goiter.

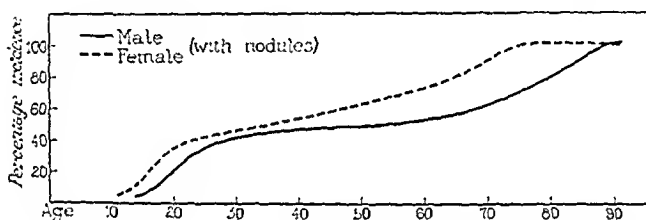


Fig. 8.—Curves showing the incidence of nodules in the thyroid gland during a life span.

Lymphocytic foci may be found in 10 per cent of the normal glands, but they are never as extensive as may be observed in an exophthalmic goiter or in an inflamed gland. Lymphoid hyperplasia is not uncommon in exophthalmic goiter and may frequently be extensive. This finding in the presence of epithelial hypertrophy and hyperplasia should be recognized as part of the picture of exophthalmic goiter and should not be confused with the exudative phase of thyroiditis (fig. 7 D). Epithelial desquamation is not found in the normal thyroid gland, whereas it is one of the characteristic features in an exophthalmic goiter.

#### CONCLUSIONS

The histologic structure of the normal thyroid gland may vary extensively. These variations are somewhat dependent on age and also on locality.

As a person passes through life the thyroid gland increases in weight, reaching its maximum during early adult life, after which it again gradually decreases to the end of the life span.

## SUBPHRENIC ABSCESS

A REVIEW OF ONE HUNDRED AND ELEVEN CASES AND A  
RÉSUMÉ OF THE SUBJECT

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This article is presented with the purpose of giving a review of 111 cases of subphrenic abscess, together with a résumé of the subject. The material was collected from 21,430 case records of patients admitted to the Jewish Hospital from 1916 to 1935 inclusive. The experience at this hospital with the extraperitoneal approach to a subphrenic abscess, with 6 deaths in 71 cases, or a mortality of 8.5 per cent, has encouraged me to present this communication, as these figures are considerably lower than those generally reported. In the twenty years that this procedure has been intermittently employed, a method of approach has been evolved which in many respects is similar to the one recently suggested by Ochsner and Graves.<sup>1</sup> There are, however, some technical differences in the procedure, detailed toward the end of this paper, which may help to simplify the approach.

The relatively good operative results obtained in the uncomplicated cases in the first decade of this study may be ascribed to the fact that the diagnosis was uncertain. During this period it was found that in the early stages of the abscess no sharp line of differentiation could be drawn between a subphrenic abscess and a perinephric abscess; but, because of their anatomic proximity, it was felt that a lumbar retroperitoneal approach could be used with advantage in either case. When the results of this method of drainage in the verified cases of subphrenic abscess were reviewed, it was found that the mortality was considerably less than that reported in the literature, and therefore in the subsequent cases of subphrenic abscess the approach was made through the lumbar extraperitoneal route. In the first decade this approach was used in 29 cases of subphrenic abscess, with 3 deaths, or a mortality of 10.4 per cent. Later (in the second decade), as the diagnosis was made earlier and attempts were made to drain the abscess promptly, other routes were tried, with comparatively poor results, necessitating a return to the extraperitoneal route. In the second decade the transserous route was used in 19 cases, with 10 deaths, or a mortality of 52.5 per cent. In this same period the extraperitoneal route was employed in

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From the Department of Surgery, the Jewish Hospital.

1. Ochsner, A., and Graves, A. M.: Subphrenic Abscess, *Ann. Surg.* 98:961, 1933.

attention of the medical profession to the condition,<sup>4</sup> culminates with Maydl's monograph<sup>5</sup> on the subject, published in 1894. Thereafter the subject attracted little attention until four years later, when Martinet<sup>6</sup> presented the results of a systematic investigation into the anatomic varieties of subphrenic abscess. This comprehensive contribution marked a distinct epoch in the study of infections in the subphrenic area and later gave impetus to Box and Eccles'<sup>7</sup> and Barnard's<sup>8</sup> anatomic subdivisions of this area. Based on these later works, Piquand,<sup>9</sup> Eisendrath<sup>10</sup> and Ochsner and his co-workers<sup>11</sup> evolved the modern conception of the management of subphrenic infections. Until recently most cases of subphrenic abscess went unrecognized, and the patient either recovered spontaneously or more frequently succumbed to the malady. With the increase in knowledge acquired from extensive abdominal and thoracic operations and with more accurate diagnostic aids, there are more cases in which the condition is recognized and treated at an early stage. It is still unfortunately true, however, that infections in the subphrenic area occur more frequently than is commonly supposed.

The terms which have been used in the literature more or less synonymously with subphrenic abscess are: perigastric abscess (Barlow), suprahepatic abscess (Bernheim), false pneumothorax (Cossy), pneumoperforative peritonitis (Sanger), hepatoperitoneal abscess (Férol), pyopneumothorax subphrenicus (Leyden), subphrenic empyema, hypophrenic abscess, subphrenic peritonitis, subdiaphragmatic abscess and others.

#### ANATOMY

The subphrenic area is limited above by the diaphragm and below by the transverse colon and its mesentery. This area is composed of two main subdivisions: an intraperitoneal area and an extraperitoneal

4. Leyden, E.: Ueber Pyopneumothorax subphrenicus, *Ztschr. f. klin. Med.* **1**:320, 1879. Pfuhl: Ein oberhalb der Leber gelegenes peritonitisches Exsudat in die rechte Lunge perforirt, mit den Zeichen eines rechtsseitigen Pyopneumothorax, *Berl. klin. Wchnschr.* **5**:57, 1877. Volkman, R., cited by Bogart.<sup>24</sup>

5. Maydl, K.: Ueber subphrenische Abseesse, Vienna, Joseph Safar, 1894.

6. Martinet, A.: Des variétés anatomiques, d'abcès sous-phrénique, Thèse de Paris, no. 84, 1898.

7. Box, C. R., and Eccles, W. M.: *Clinical Applied Anatomy*, Philadelphia, P. Blakiston's Son & Co., 1906.

8. Barnard, H. L.: Surgical Aspects of Subphrenic Abscess, *Brit. M. J.* **1**: 371 and 429, 1908.

9. Piquand, G.: Les abcès sous-phréniques, *Rev. de chir.* **39**:156, 1909.

10. Eisendrath, D. N.: Complications of Appendicitis, *S. Clin., Chicago* **1**: 1035, 1917.

11. (a) Ochsner, A.: Subphrenic Abscess: Its Diagnosis and Treatment, with Special Reference to the Extraperitoneal Operation, *Internat. Clin.* **2**:79, 1931. (b) Ochsner, A.; Gage, I. M., and Garside, E.: The Intra-Abdominal Post-Operative Complications of Appendicitis, *Ann. Surg.* **91**:544, 1930.

abdominal wall below the diaphragm (this area may be arbitrarily divided into a right and a left side by a midabdominal line); (2) the right posterior extraperitoneal area, located between the posterior external surface of the parietal peritoneum and the upper posterior abdominal wall below the diaphragm and to the right of the inferior leaf of the coronary ligament (this area includes the bare area of the liver), and (3) the left posterior extraperitoneal area, located between the posterior external surface of the parietal peritoneum and the upper posterior abdominal wall below the diaphragm and to the left of the inferior leaf of the coronary ligament.

*Subdivisions.*—The literature deals adequately with the anatomic subdivisions of the intraperitoneal area. However, subdivisions of the extraperitoneal area have received almost no consideration. It is the

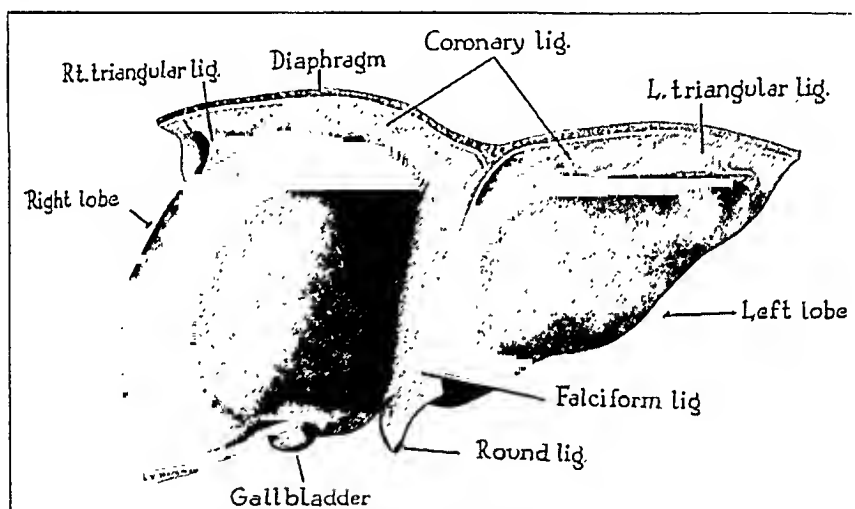


Fig. 2.—The liver, showing its ligamentous attachments which subdivide the suprahepatic subphrenic area. The diaphragm and its peritoneal attachments and reflections above the liver are shown in detail.

further purpose of this paper to call the reader's attention to these subdivisions and to point out the sources, the location and the incidence of infections of the extraperitoneal areas (see table 3). Many investigators refer to an "extraperitoneal" area, having in mind only the region of the bare area of the liver.

#### ETIOLOGY

Subphrenic abscess usually follows a suppurative process elsewhere in the body and generally one in the abdomen. It is rarely primary. Schwartz<sup>12</sup> reported 8 cases of so-called primary subphrenic abscess,

12. Schwartz, J.: Suppuration in the Subphrenic Region, with Special Reference to Primary Idiopathic Liver and Subphrenic Abscess, *Arch. Surg.* 20:317 (Feb.) 1930.

Infections of the subphrenic area following appendicitis may take place: (a) as a result of a generalized peritonitis secondary to a ruptured appendix, (b) as a result of an abscess of the liver following an infected thrombophlebitis arising from the appendix, (c) through infection of the posterior cellular spaces, (d) through the lymphatics, and (e) as a result of an ascending infection extending along the paracolic gutter.

(a) The first type has been considered under section 1.

(b) The second type will be considered under section 3.

(c) Aschoff<sup>13</sup> has shown that there are four layers of lymphatics in the wall of the appendix, all of which drain into the meso-appendix. Munro<sup>14</sup> pointed out that infections in the lymphatics of the meso-

TABLE 2.—*Etiology of 111 Subphrenic Abscesses*

Organ	Number of Cases	Total Percentage
Stomach and duodenum.....	6	5.4
Gastric ulcer with perforation.....	4	3.6
Perforated carcinoma of the stomach.....	1	0.9
Perforated duodenal ulcer.....	1	0.9
Appendix.....	26	23.4
With generalized peritonitis.....	13	11.7
Liver and biliary passages.....	33	34.2
Abscess of liver.....	3	2.7
Diseases of the biliary passage with localized peritonitis at the time of operation on the biliary passage.....	13	11.7
Kidney.....	5	4.5
Female genitalia.....	2	1.8
Pelvic abscess.....	6	5.4
Prostatic abscess.....	1	0.9
Intestine.....	1	0.9
Empyema.....	1	0.9
Pneumonia.....	3	2.7
Abscess of the lung.....	1	0.9
Typhoid of the spine.....	1	0.9
Furunculosis.....	1	0.9
Grip.....	2	1.8
Unknown causes.....	17	15.3

appendix may be carried back to the retroperitoneal cellular space above and behind the cecum. From here the infection spreads up into the retroperitoneal cellular spaces behind the ascending colon and in front of the kidney to the subdiaphragmatic space. If, in addition, the appendix is under the liver or is retrocecal or associated with an abscess, the possibilities of the formation of a subphrenic abscess are greatly enhanced. Frequently, in the removal of an inflamed appendix which is adherent to the posterior parietal peritoneum, the appendix is torn away from its attachments, leaving a piece of infected necrotic tissue behind, or a part of the surface of the peritoneum is pulled away with the appendix. In either case a raw and infected surface is left through

13. Aschoff, L.: *Appendicitis: Its Aetiology and Pathology*, translated by G. C. Pether, London, Constable & Co., Ltd., 1932.

14. Munro, J. C.: Lymphatic and Hepatic Infections Secondary to Appendicitis, *Ann. Surg.* 42:692, 1905.

the pleural contents to enter the subdiaphragmatic space, or (2) by an infection producing a lymphatic block in the chest, which extends back to the subphrenic area. (This phase will be considered in detail under the heading "4. Retrograde Lymphatic Infection from the Thorax.") In the present series of cases of known etiology, 5 (5.3 per cent) were due to rupture into the subphrenic area.

4. *Retrograde Lymphatic Infection from the Thorax.*—Schlanger<sup>20</sup> injected a radiopaque material into the subphrenic area and studied its spread through the lymphatics by means of roentgenograms. He was able to show retropleural lymphatic extensions into the hilar area of the lung. In the case of a subphrenic abscess secondary to empyema thoracis, pneumonia, abscess of the lung, etc., the thoracic lymphatics which communicate with the subphrenic area become infected. As a result of the lymphatic blockage which is set up, retrograde stagnation and infection take place. This process extends as far back as the dilated lymphatics on the inferior surface of the diaphragm. The lymphatics become increasingly distended with the infected material until they rupture, thereby producing an infection of the subphrenic area. In the present series of cases of known etiology, 5 (5.3 per cent) were due to retrograde lymphatic infections.

5. *Metastatic Infection.*—The existence of an infection which finds its way into the blood stream is presupposed. The infection is then carried to and deposited in the subphrenic area via the circulation. Such cases occur following furunculosis, osteomyelitis, septicemia, grip, etc., and are reported in the literature from time to time. In the present series of cases of known etiology, 3 (3.2 per cent) were due to metastasis.

6. *Direct Implantation.*—In cases of direct implantation, the subphrenic area is injured, as in a stab wound or gunshot wound of the lower part of the thorax or the upper part of the abdomen. Infection is carried into the subphrenic area with the traumatizing instrument, or the injury may have been sustained by an organ anatomically related to the subphrenic area, which, as a result of the injury, becomes a locus minoris resistentiae and subsequently ruptures into the subphrenic area. Injuries to the base of the lung, diaphragm, stomach and liver are included in this group. Although subphrenic abscess due to trauma is rare, it has been reported. In the present series of cases of known etiology, there were none due to trauma.

*Summary.*—Of Ochsner and Graves'<sup>1</sup> series of cases of subphrenic abscess, including those collected from the literature, 29.1 per cent arose from an infection in the stomach and duodenum, 30.6 per cent

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20. Schlanger, P.: Las vías linfáticas del espacio subfrénico derecho, Rev. méd. latino-am. **13**:2244, 1928.

found most frequently associated with other organisms—in 10 (14.4 per cent) of the cases. Barnard<sup>8</sup> and Whipple<sup>21</sup> reported the bacteriologic findings in a total of 44 cases in which series they found colon bacilli in 36 per cent of the cases, streptococci in 22.5 per cent and staphylococci in 15.8 per cent.

Cokkins<sup>22</sup> stated:

It is surprising to find that Ochsner and Graves report this space [the right infrahepatic intraperitoneal] to have a less number of collections than the posterior, superior space. The explanation possibly is that most of the infections in this space subside more often than in the other spaces.

In Ochsner and Graves' series of cases collected from the literature the right posterior suprahepatic area was involved in 28.86 per cent and

TABLE 4.—*Organisms in 70 Cases of Subphrenic Abscess*

Organism	Number of Cases	Total Percentage
<i>Bacillus coli</i> .....	22	31.4
<i>Streptococcus</i> .....	21	30.2
Nonhemolytic streptococcus.....	11	15.7
<i>Streptococcus haemolyticus</i> .....	9	12.9
<i>Streptococcus viridans</i> .....	1	1.4
<i>Staphylococcus</i> .....	22	31.4
<i>Staphylococcus aureus</i> .....	13	18.6
<i>Staphylococcus albus</i> .....	9	12.8
<i>Pneumococcus</i> .....	4	5.7
<i>Bacillus mucosus-capsulatus</i> .....	2	2.8
<i>Micrococcus catarrhalis</i> .....	1	1.4
<i>Bacillus subtilis</i> .....	1	1.4
Gram-positive diplococcus and coccus.....	6	8.6
Gram-positive bacillus.....	1	1.4
Gram-negative bacillus.....	2	2.8
Organisms undetermined.....	10	14.3
More than one organism present.....	22	31.5

the right infrahepatic area in 8.9 per cent. In their own 50 cases, the right posterior suprahepatic area was involved in 60 per cent and the right infrahepatic area in 13.5 per cent. In the present series of 90 cases in which operation was performed the right posterior suprahepatic area was involved in 20 per cent and the right infrahepatic area in 35.5 per cent. While my statistics corroborate the view held by Cokkins, but those of Ochsner and Graves do not, I am of the opinion that the explanation offered by the former is not entirely warranted. According to Ochsner and Graves' statistical résumé and the opinion of many other investigators, the stomach and duodenum, the appendix and the liver and biliary passages constitute the three greatest sources of sub-

21. Whipple, A. O.: A Study of Subdiaphragmatic Abscess, *Am. J. Surg.* **40**: 1, 1926.

22. Cokkins, A. J., in Maingot, R.: *Post Graduate Surgery*, New York, D. Appleton-Century Company, Inc., 1936, vol. 1.

phrenic abscesses. Therefore a discussion of these three sources may help explain the aforementioned difference of opinion.

It is not unlikely that in a goodly proportion of the cases of subphrenic abscess of gastric origin collected by Ochsner and Graves the original lesion was in the region near the pylorus. In such cases, as well as in those of duodenal origin, a greater number of the abscesses occur in the right infrahepatic area than in the right posterior suprahepatic area. It is generally agreed that an appendical pathologic process is more often followed by involvement of the right posterior suprahepatic area than of the right infrahepatic area and that a pathologic process of the liver and biliary passage is more often followed by involvement of the right infrahepatic area than of the right posterior suprahepatic area. Taking this into consideration and the percentage of cases presented in which the abscess originates from a lesion in these organs, one sees that in Ochsner and Graves' cases the right posterior suprahepatic area should be involved more often than the right infrahepatic area and the right infrahepatic area more frequently than the right posterior suprahepatic area. Thus, any group of cases will give statistical results which are dependent generally on the proportion in which these three groups of sources are represented.

A subphrenic abscess secondary to appendicitis may first be located in the right infrahepatic area, as Cokkins suggested, and then extend up to the right posterior suprahepatic area, and at this time necessitate operation. Evidence of subsiding infection of the infrahepatic area following appendectomy, with activity in the right posterior suprahepatic area, was found in 3 (3.3 per cent) of the cases in the present series in which operation was performed. It is therefore the source and the time after onset at which the patient is seen which will ultimately determine the location of the infection.

#### CLINICAL MANIFESTATIONS

The multiplicity and variety of complaints usually attending a subphrenic abscess make it difficult to present a classic picture of the condition. A difference in etiology, age of the patient, location of the abscess and duration of the illness will help to alter the clinical picture. Regardless of the factors influencing the origin of a subphrenic abscess, the mode of onset will always take one of three characteristic forms: (1) sudden, (2) insidious or (3) postoperative.

*Sudden Onset.*—When the abscess is of sudden onset it simulates a perforated peptic ulcer (more commonly a gastric) with generalized peritonitis. There is a sudden pain in the epigastrium, vomiting, prostration, difficulty in taking a deep breath, a sensation of fulness in



*General or Systemic Manifestations.*—The onset may be vague, with malaise, fatigue, loss of appetite and pallor, accompanied by a dull ache in the region of the abscess. As the condition progresses, the temperature and pulse become elevated and fluctuant. The patient has chills and sweats profusely. Nausea and vomiting usually have made their appearance before this stage, if the lesion is intraperitoneal, and particularly if the onset is acute. As the condition advances, the patient loses weight and complains of pain in the corresponding shoulder and in the region of the abscess, and occasionally hiccups or belching develops. At times there are associated jaundice and severe anemia. The white blood count rises to about 22,000, with 85 per cent polymorphonuclear leukocytes. On examination one finds an acutely sick patient with a hectic flush, a warm moist skin, a short hacking cough, an anxious expression, dyspnea and breathing restricted on one side. There may also be seen a bulging area below the costal margin in the abdomen or bulging edematous interspaces or a mass in the lumbar region.

*Examination of the Chest.*—During respiration that side of the chest which is involved moves little if at all. The interspaces become widened and bulge. There is a tendency to flaring of the wall of the lower part of the chest in the posterior axillary area. If the abscess is deeply placed, there is retraction of the interspaces rather than widening. The costal arch is tender to pressure in this area. On percussion, there is impairment over the lower part of the chest, and the diaphragm is elevated and fixed in that position. If the abscess is in the anterior infrahepatic area, there is tenderness along the tenth rib anteriorly. If the abscess is in the right posterior suprahepatic area, there is tenderness along the twelfth rib posteriorly. The breath sounds in the area of impaired percussion are distant or entirely suppressed. Occasionally with partial compression of the lung, one hears transmitted bronchial breath sounds in the upper area of impaired percussion. If the abscess contains gas, signs suggesting pneumothorax may be obtained. A friction rub may be heard at the lower part of the thorax. This is not a pleural rub, as was formerly believed, but is due to the diaphragm rubbing against the inflamed upper surface of the liver. If the abscess is on the left side, the heart will be pushed upward or tilted to the right but will not be displaced to the right. When the abscess is on the left side one occasionally hears a peculiar clicking quality to the second heart sound at the apex. To differentiate between subphrenic abscess and empyema thoracis, it should be noted that in empyema the upper limit of the fluid is concave, whereas in subphrenic abscess it is convex (DaCosta<sup>23</sup>). The onset in 45 per cent of the cases in the present series was referable to the thorax.

23. DaCosta, J. C.: *Modern Surgery, General and Operative*, Philadelphia, W. B. Saunders Company, 1931.

LeWald,<sup>26</sup> Pancoast<sup>27</sup> and Granger<sup>28</sup> have shown that by far the greatest single aid in helping to make a diagnosis of subphrenic abscess is a series of well taken roentgenograms. These should be taken in all directions—anteriorly, laterally, obliquely and posteriorly. They should be taken with the patient in the erect and in the prone position and during inspiration and expiration. In the presence of a subdiaphragmatic collection, such plates will show the elevated motionless diaphragm, a small amount of fluid in the costophrenic sinus and the heart pushed up or tilted to the opposite side. Underneath the diaphragm there is a dense shadow or a gas bubble, which at times is above a distinct fluid level. Frequently only a few of these findings are present; however, there are sufficient to make one highly suspicious of a subphrenic collection, but a pleural effusion cannot be ruled out. In such cases Lilienthal suggested pneumoperitoneum to outline the area between the liver and the diaphragm, thereby helping to localize the site of the collection.

An early subphrenic abscess produces a somewhat ill defined clinical picture, which, with the past history and roentgenographic studies, should not be difficult to recognize. That the diagnosis will be overlooked if it is not kept in mind is shown by Overholt's<sup>29</sup> case, in which the diagnosis was not made until six months had elapsed, and by Lockwood's<sup>30</sup> case, in which the diagnosis was not made until twenty months after the onset. In the present series of cases there were 18 (16.2 per cent) in which the diagnosis was not made until four or more months after the onset. In one of these cases seven years had elapsed before the diagnosis was made. In another one of the cases, three months after an appendectomy for a ruptured retrocecal appendix the patient was readmitted to the hospital with vague, persistent pain in the right side of the upper part of the abdomen. A diagnosis of chronic cholecystitis was made, and the gallbladder was removed. Before the operation, a roentgogram of the chest showed the diaphragm to be high on the right side. After operation the position of the diaphragm was unchanged, and the patient stated that she "felt worse

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26. LeWald, L. T.: Subphrenic Abscess and Its Differential Diagnosis Roentgenologically Considered, *Arch. Surg.* **10**:544 (Jan.) 1925.

27. Pancoast, H. K.: The Roentgenological Diagnosis of Liver Abscess With or Without Subdiaphragmatic Abscess, *Am. J. Roentgenol.* **16**:303, 1926.

28. Granger, A.: Radiological Signs of Subdiaphragmatic Abscess, *New Orleans M. & S. J.* **82**:748, 1930.

29. Overholt, R. H.: Subphrenic Abscess with Extension into the Right Lung and Cure by Phrenic Exeresis, *S. Clin. North America* **12**:619, 1932.

30. Lockwood, A. L.: Subdiaphragmatic Abscess, *Surg., Gynec. & Obst.* **33**:502, 1921.

(5) pneumonia or pneumonitis, (6) pericarditis, (7) mediastinal abscess, (8) pneumothorax or pyopneumothorax and (9) perforation of the abdomen.

1. Pleural effusion is variously estimated to be present in from 9 to 100 per cent of cases. It was a complication in 30 (36 per cent) of the cases in the present series.

2. Empyema may develop as a later complication of pleural effusion or as a direct infection of the pleural space. Organisms may enter the pleural space either through the lymphatics from below the diaphragm or by a subphrenic abscess rupturing into the pleural space; or empyema may develop in a patient with a subphrenic abscess in whom an abscess of the lung, pneumonia or sepsis is developing as a secondary condition. Empyema following a subphrenic abscess has been variously estimated as occurring in from 11.9 to 42.5 per cent of cases. It was found in 16 (19.2 per cent) of the cases in the present series.

3. Bronchopleural fistula per se does not occur. It is usually secondary to empyema, pneumonia or abscess of the lung. Bronchopleural fistula secondary to subphrenic abscess and its sequelae has been variously estimated to occur in from 5 to 20 per cent of cases. It was found in 4 (4.7 per cent) of the cases in the present series.

4. Abscess of the lung is usually the result of a lymphatic extension into the lung, postpneumonic or embolic in origin. Abscess of the lung following a subphrenic abscess has been variously estimated as occurring in from 6 to 16 per cent of cases. It was found in 8 (9.6 per cent) of the cases in the present series.

5. Pneumonia or pneumonitis is either a superimposed infection or an extension of the process from below the diaphragm to the lung. The incidence of pneumonitis following subphrenic abscess has been variously reported as being from 5.9 to 33.3 per cent. It was found in 10 (12 per cent) of the cases in the present series.

6. Pericarditis is usually the result of a lymphatic extension of the infection from below the diaphragm, especially on the left side, or from empyema, pneumonitis or abscess of the lung. The incidence of pericarditis following subphrenic abscess has been variously reported as being from 6 to 20 per cent. It was found in 2 (2.4 per cent) of the cases in the present series.

7. Mediastinal abscess may result from the breakdown of infected mediastinal glands or as a direct extension into the mediastinum from a subdiaphragmatic abscess, or from pneumonitis, which in turn is due to a subdiaphragmatic abscess. The incidence of mediastinal abscess following subphrenic abscess has been variously reported as being from 2.9 to 7 per cent. It was not seen in the present series of cases.

wood) to 100 per cent in those in which it was not performed (Deaver). With the newer conception of the management of a subphrenic abscess, the mortality has dropped to about 25 per cent. Even this mortality is too high but is in part due to surgically uncontrollable factors, such as preoperative peritonitis, ruptured appendix, perforated peptic ulcer, etc. In the series of 111 cases studied there were 24 deaths, or a total mortality of 21.6 per cent. In the 90 cases in which operation was performed there were 16 deaths, or a mortality of 17.6 per cent. In the 21 cases in which operation was not performed there were 8 deaths, or a mortality of 38.4 per cent.

It is universally agreed that all things being equal, the highest mortality is obtained in transperitoneal drainage of a subphrenic abscess and the lowest, in extraperitoneal drainage of the abscess. The mortality is distinctly lower in those cases in which drainage has been instituted without contamination of a serous cavity. In the present series of cases the mortality for those in which extraperitoneal drainage was instituted (71 cases) was 8.5 per cent whereas for those cases (7) in which transpleural drainage was instituted it was 42.6 per cent and for those (12) in which transperitoneal drainage was used it was 58.1 per cent. In Ochsner and Graves' <sup>1</sup> series of cases collected from the literature, the mortality from extraperitoneal drainage was 21 per cent, that from transpleural drainage was 39 per cent and that from transperitoneal drainage was 35.5 per cent. The mortality in all patients between the ages of 20 and 50 years was highest. In this study the mortality for the group of patients below 20 years of age was 15 per cent, that for the group between the ages of 20 and 50 years, 65 per cent, and that for the group between the ages of 50 and 70 years, 20 per cent. Barnard <sup>8</sup> reported similar mortalities on the basis of age.

#### TREATMENT

The treatment may be considered under: (a) prophylaxis, (b) conservative care and (c) operation.

*Prophylaxis.*—A considerable number of subphrenic abscesses subside spontaneously. Therefore, efforts should be directed toward accomplishing this end, and at the same time an effort should be made to decrease the severity of those abscesses which occur in spite of prophylactic care. Prophylaxis begins with the early institution of surgical care for a suppurative process or for a perforated viscus. In the operating room it consists of carefully walling off the pathologic area, so as to avoid the spread of infectious material, and, similarly, careful handling of the viscera, so as to avoid squeezing infectious material out of them, and, finally, the avoidance of traumatization while removing an offending cause. At the termination of the surgical procedure

The extraperitoneal approach is recommended as the method of choice, because the peritoneum is more readily separated from the diaphragm than from the pleura. This approach may be made either anteriorly or posteriorly.

The posterior extraperitoneal approach (on the right side) is illustrated in figures 3, 4 and 5.

A description of the technic follows:

The patient lies on the uninvolved side, with the lower part of the chest raised by a kidney rest, so that the lower dorsal portion of the spine is convex upward. The legs are drawn up and flexed on the abdomen, and the body is inclined slightly forward. Local or paravertebral block anesthesia is used. A transverse incision is made at the level of the middle of the first lumbar vertebra, beginning in the

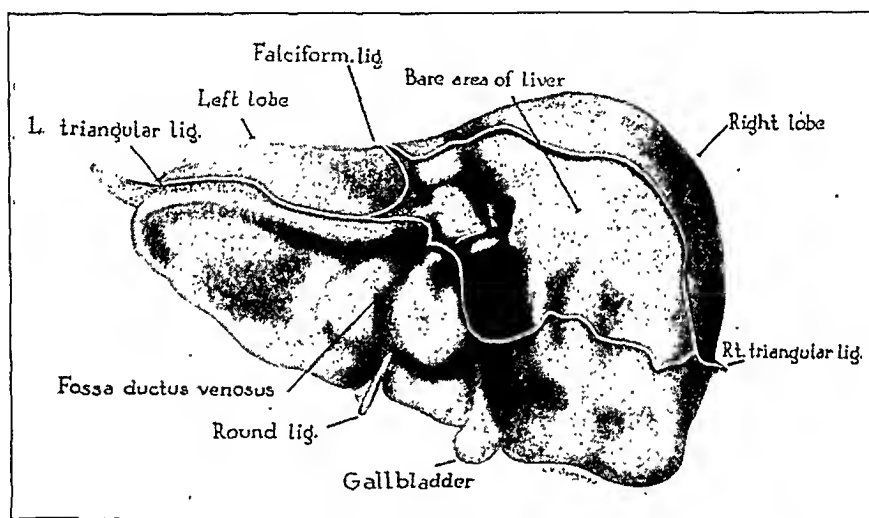


Fig. 3.—The liver seen from behind and partly rotated forward to expose the upper posterior surface and part of the inferior surface. This view also shows the peritoneal reflections and ligamentous attachments of the liver and the bare area of the liver.

posterior axillary line, and is carried backward to the paravertebral area. The twelfth rib is exposed and resected subperiosteally. The erector spinae muscles are retracted medially without cutting them. The original incision is then carried deeply through the bed of the twelfth rib, thereby avoiding the costophrenic angle and the pleura. The spinal attachments of the diaphragm at this level are severed, and the perinephric fascia is exposed. This fascia is gently pushed inward and downward, as is the kidney, until the lower edge of the liver is felt. This exposes the right infrahepatic area and the peritoneum. The infrahepatic area is palpated for induration. If present, the area is aspirated. If pus is obtained, the area is opened by means of the exploring finger. If no pus is obtained the peritoneum on the inferior surface of the diaphragm is gently pushed away until the region about the right posterior suprahepatic area is reached. Before the abscess is reached, an area of induration will be palpable. This area is aspirated, and if pus is present the finger is manipulated into the abscess. A large black rubber

drainage tube, with a cigaret drain on either side of it, is inserted into the abscess cavity and exteriorized through the wound in the skin, to which all three are fixed. If no pus is obtained on aspiration, the subdiaphragmatic peritoneum is further decollated until the extraperitoneal area is reached. This area is aspirated, and if pus is obtained the abscess is treated as suggested previously. Through this incision, the right infrahepatic and the right posterior suprahepatic intraperitoneal areas and the right posterior extraperitoneal area may be reached and drained. Considering that this procedure will reach about 65 per cent of the subphrenic abscesses, it cannot be too highly recommended. On the left side the best approach is via the left posterior infrahepatic area.

The technic for the anterior extraperitoneal approach follows:

An incision is made below the costal margin and parallel to it, on the affected side. The tissues are separated down to the parietal peritoneum. By finger dissection the peritoneum is mobilized from the inferior surface of the diaphragm until an indurated area is felt. This is aspirated, and if pus is obtained, the finger is gently pushed into the area. The pus is then evacuated, and the abscess cavity is drained in the manner previously described. The anterior extraperitoneal approach is a good one, and for those abscesses localized in the right anterior suprahepatic area and the right infrahepatic area it will best meet the surgeon's requirements. On the left side it is ideal for collections of pus in the anterior infrahepatic and suprahepatic areas, as well as a good approach for the infections of the anterior extraperitoneal area.

Occasionally, an intraperitoneal abscess becomes adherent to the parietal peritoneum, and localization takes place under it, with local obliteration of the peritoneal space. In such instances one is at liberty to open the abscess and drain it in the usual manner employed for any localized abscess. The local reaction has sealed off the peritoneum, preventing its contamination.

In those cases in which there is a coexisting empyema, drainage via the extraperitoneal route is contraindicated. In all likelihood the diaphragm is perforated, and therefore thoracotomy should be done, the opening in the chest being made large enough to allow exploration of the diaphragm. The diaphragm is explored, and if the perforation is found, the subphrenic abscess and the empyema are drained, separate drains being employed. If the abscess is not found and one is certain that a subphrenic abscess is present, the diaphragm is nicked in the direction of its fibers, over the site of the abscess. A black rubber drain is inserted into the abscess cavity and exteriorized with the empyema tube through the wall of the chest, to which the tubes are fixed.

#### SUMMARY AND CONCLUSIONS

I have endeavored to present a general résumé of the etiology, course and treatment of subphrenic abscess, together with a review of 111 cases. I advocate surgical intervention suited to the conditions present and feel that the extraperitoneal route is the ideal one in most types of

# TREATMENT OF TUMOR OF THE PAROTID GLAND

SURVEY OF THE RESULTS OBTAINED AT THE BARNARD  
FREE SKIN AND CANCER HOSPITAL

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The present status regarding the etiology of tumor of the parotid gland, which for many years was the subject of a lively academic discussion, has been summarized by Ewing<sup>1</sup> as follows:

1. The endothelial origin has been disproved.

2. No single source of mixed tumor meets all requirements. Some are distinctly adenomatous and probably arise from the acini and the ducts of the gland in which they are well incorporated. Others are encapsulated or extraglandular, and take the form of basal cell or adenocystic epithelioma. These probably arise from misplaced and occasionally embryonal portions of gland tissue. Branchial remnants may possibly be connected with this group.

3. The derivation of mucous tissue and cartilage from gland epithelium has been satisfactorily proved, and there is no necessity of including in the originating tissue any cartilaginous structures.

McFarland,<sup>2</sup> reporting a series of ninety cases of tumor of the parotid gland in 1926, differed somewhat from Ewing in that he expressed the belief that the theory of enclavement or embryonal sequestration affords the most satisfactory explanation of the origin of this type of tumor. He also stated that the tumor has no relationship to the normal structures in which it occurs but from which it does not arise.

That the majority of mixed tumors are benign and if completely removed do not tend to recur is conceded by nearly all authorities. However, if a tumor does recur it may become progressively more invasive without giving rise to distant metastases and may cause the death of the patient. The problem of malignant change in a simple mixed tumor does not have the universal support that the concept of the simple mixed tumor itself possesses. Some investigators believe that there is a certain percentage of simple mixed tumors which undergoes malignant degeneration.

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From the Surgical Service of Dr. William E. Leighton.

1. Ewing, J.: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 775.

2. McFarland, Joseph: *Ninety Tumors of the Parotid Region*, *Am. J. M. Sc.* **172**:804, 1926.

Wood<sup>10</sup> recommended surgical intervention as the proper treatment and advised that it be done early. Most failures, he asserted, are due to the complicating anatomic relationship of the facial nerve.

Jackson<sup>11</sup> concurred in recommending early operation in cases of mixed tumor.

Blair and Olch advised early removal of a tumor of the parotid gland together with a portion of the normal gland superficial to the facial nerve.

McFarland, in his report of 1933, drew some rather pessimistic conclusions regarding treatment. Except for improvement in appearance or to ease the patient's mind, he stated that it would be just as well not to operate. He differed from other observers in that he cautioned against the removal of small tumors, as he considered that they are likely to recur. Operation, he stated, has done little for the malignant tumor of the parotid gland, while irradiation is of no benefit. If operation is decided on, he stated that there is no hurry and that due consideration should be given the possible accidents, namely, facial paralysis and salivary fistula.

The role played by irradiation in the treatment of a tumor of the gland is at present a matter of controversy. Benedict and Meigs stated that in their series roentgen and radium therapy have been beneficial as a palliative measure only. Geschickter and Stein also reported that irradiation is beneficial as a palliative measure in cases of malignant tumor. They also applied irradiation postoperatively to the bed of the tumor.

Merritt<sup>12</sup> stated that the treatment of a mixed tumor is largely in the hands of the radiologist and that although a small tumor may be excised, radium will accomplish the same results. He further stated that a combination of irradiation and surgical treatment is illogical; if one is sufficient, the other is superfluous.

Widman,<sup>13</sup> reporting his results in 54 cases of tumor of the parotid gland, of which 35 were malignant and 19 were benign, stated that the roentgen rays have shown no appreciable effect on clinically benign tumors. No clinical cures have been obtained in 27 cases of advanced primary and recurrent inoperable malignant tumors. The palliative effect of the roentgen rays and radium were sufficient to justify recommending them for this purpose.

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10. Wood, Francis C., in *Nelson Loose Leaf Living Surgery*, New York, Thomas Nelson & Sons, 1927, vol. 2, p. 112.

11. Jackson, A. S.: *Mixed Tumors of the Parotid Gland*, Wisconsin M. J. **31**:701, 1932.

12. Merritt, E. A.: *Mixed Tumors of the Parotid Gland*, Am. J. Roentgenol. **25**:507, 1931.

13. Widman, B. F.: *The Treatment of Parotid Tumors with Roentgen Rays and Radium*, J. M. Soc. New Jersey **31**:95, 1934.



# Summary of Data on Mixed Tumors and Malignant Tumors of the Parotid Gland

Type of Tumor	Number of Cases	Number of Tumors Treated	Number in Males	Number in Females	Right Side	Left Side	Not Stated	Average Age, Yr.	Average Duration, Yr.	No Recurrence
Mixed tumors.....	34	18	9	25	23	11	..	47.32	11.02	10*
Malignant tumors.....	36	23	22	13	15	19	2	53.33	2.72	6†

SUMMARY OF TREATMENT USED										
Types of Treatment Used for Mixed Tumors ‡					Types of Treatment Used for Malignant Tumors					
Simple excision .....	14	Radical operations .....	9	Radical operations .....	2					
Radical excision .....	1	Radical operation plus 1,200 mg. hours radium... 1	1	Local excision .....	1					
Excision by cautery plus 20 radon seeds.....	1	Cautery excision .....	1	Local excision .....	1					
Radon seeds .....	1	Local excision of gland plus ascending ramus of mandible .....	1	Excision by cautery.....	1					
Excision and radium element.....	1	Local excision plus cautery to the surface.....	1	Local excision plus resection of mandible.....	1					

DATA ON UNTREATED TUMORS										
Mixed Tumors					Malignant Tumors					
Date	Age of Patient, Yr.	Sex of Patient	Duration of Tumor	Side	Age of Patient, Yr.	Sex of Patient	Duration of Tumor	Side	Microscopic Diagnosis	
5/ 4/31	78	M	8 yr.	R	5/23/32	F	4 mo.	R	Carcinoma of parotid gland	
2/ 2/32	47	F	5 yr.	L	1/19/22	F	6 yr.	R	None	
5/15/32	68	M	15 yr.	R	12/16/23	M	6 mo.	R	None	
5/12/30	38	F	9 yr.	L	2/13/24	M	10 yr.	R	None	
5/19/26	45	F	13 yr.	L	4/23/24	F	2 mo.	R	None	
2/26/26	64	F	42 yr.	R	12/28/31	M	11 mo.	R	None	
10/26/16	67	M	35 yr.	R	1/26/32	M	6 yr.	L	None	
10/17/30	74	M	18 mo.	L	9/26/11	F	3 yr.	R	None	
2/16/26	35	F	6 yr.	R	9/15/14	F	2 yr.	L	None	
5/23/32	67	F	4 mo.	R	1/14/15	M	?	R	None	
1/29/34	44	F	21 yr.	R	6/20/34	F	6 mo.	R	Biopsy; squamous cell carcinoma, Grade II	
3/19/34	38	F	10 yr.	R	4/22/35	M	5 mo.	L	None	
5/ 8/35	48	F	20 yr.	R	10/16/35	F	2 mo.	L	None	
2/24/36	72	M	2 mo.	R						
4/ 6/36	49	F	6 mo.	R						
4/24/36	47	F	2 yr.	R						

DATA ON TREATED TUMORS										
Malignant Tumors—Surgical Treatment					Microscopic Diagnosis					
Date	Age of Patient, Yr.	Sex of Patient	Duration of Tumor	Side	Treatment	Microscopic Diagnosis	Follow-Up Study			
11/ 7/32	42	F	6 mo.	R	Radical operation	Malignant mixed tumor with metastasis	12/ 7/34: Recurrence; also cancer of uterus			
2/ 2/23	52	M	25 yr.	L	Radical operation	Malignant mixed tumor	7/19/23: Recurrence in flap			
12/10/23	59	M	6 mo.	L	Radical operation	Malignant mixed tumor	7/ 6/24: Died of cancer			
9/ 8/24	70	M	3 mo.	R	Local excision plus 800 mg. hours of radium	Malignant mixed tumor	1925: Died of cancer			

out that this patient had a recurrent tumor when she first came into the clinic. One patient was treated with excision plus 200 mg. hours of radium element, and at the last observation, six weeks after treatment, no recurrence was noted.

Among the patients treated at the hospital "no recurrences" has been reported as soon as six weeks postoperatively, as it is stated that recurrences usually occur immediately. On the other hand, it has been shown that they may occur as late as thirty years, and hence one should hesitate in declaring any patient cured.

There were 36 patients with malignant tumors of the parotid gland noted in the group at the Barnard Hospital. Of these 17 were treated surgically, 6 were treated by radiation and 13 received no treatment of any kind. In the group treated surgically, microscopic sections showed 14 malignant mixed tumors and 3 squamous cell carcinomas. Biopsy was done in only 2 of the 6 cases in which irradiation was employed. However, the diagnoses in the remaining 4 was correct because the patients had recurrences or died of the tumor. Biopsy specimens were obtained from only 2 of the untreated malignant tumors. The age of the patients in this group varied from 31 to 84, with an average of 58.33 years, while the duration of the tumor varied from one month to twenty-five years, with an average of two and seventy-two one-hundredths years. There were 22 males and 13 females in the group, and in 1 case the sex was not stated. Fifteen tumors were located on the right side and 19 on the left. In 2 cases the records did not state on which side the tumor was located. The type of surgical treatment which was used varied. In 9 instances a radical operation was employed, i. e., excision of the entire parotid gland to the pharyngeal wall, together with dissection of the tributary lymphatics of the neck. In 2 of these 9 cases there was no evidence of recurrence in fifty-seven months and two months, respectively. The remainder of the patients have died of the disease or show advanced recurrence. One patient underwent the radical operation, and received in addition 1,200 mg. hours of radium, and when last seen, one year after operation, showed no evidence of recurrence. In 2 instances, local excision was used, once with a knife and once with cautery, and in addition radium was applied to the bed of the tumor. Both patients have since died of tumor. Two patients received local excision alone. One died of the tumor, while the other showed no evidence of recurrence in fifty-three months. One tumor was excised by cautery, with no evidence of recurrence in forty-eight months. In another instance simple excision was used, with the application of the actual cautery to the bed of the tumor. This patient later died of cancer. Local excision of the gland, together with a portion of the ascending ramus of the mandible, was

# MECKEL'S DIVERTICULUM

## ITS INCIDENCE AND SIGNIFICANCE IN ROUTINE OPERATIONS ON THE ABDOMEN

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A review of the literature on Meckel's diverticulum and a search through the surgical files of the New York Post-Graduate Medical School and Hospital reveal a particular significance to the finding of this congenital anomaly at routine operations on the abdomen—a significance not so striking because of the incidence of the anomaly as in its production of symptoms which mimic those of other acute abdominal conditions. In but comparatively few instances has a diverticulum been the specific surgical indication, and all too frequently the symptom complex of acute diverticulitis has been interpreted in terms of other gastrointestinal conditions.

Since first described by Johann Friedrich Meckel in 1809<sup>1</sup> and 1812,<sup>2</sup> numerous records of the occurrence of the diverticulum have been made, but it appears to have been encountered in most cases as an incidental finding during laparotomy or at necropsy. This point of view is borne out by recent personal communications from surgeons of large experience who state that an increasing number of diverticula have been found since routine examination of the distal segment of the ileum is being made; in other words, since surgeons have become "diverticulum minded."

### EMBRYOLOGY

The (vitelline) omphalomesenteric duct usually begins to atrophy during the early weeks of fetal life and normally should disappear. Complete obliteration, however, may fail anywhere along the course of the duct. Persistence of the proximal segment manifests itself as

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Read before the New York Academy of Medicine, Section of Surgery, Jan. 8, 1937.

1. Meckel, Johann Friedrich: Ueber die Divertikel am Darmkanal, *Arch. f. d. Physiol.* 9:421-453, 1809.

2. Meckel, J. F.: *Handbuch der pathologischen Anatomie*, Leipzig, C. H. Reclam, 1812, vol. 1, p. 579; cited by Burger.<sup>15</sup> (The original German article was not available at the library of the New York Academy of Medicine, although translations into French, and into English from the French, are obtainable.)

to the ileocecal junction, its exact location depending on variations in the development of the limbs of the umbilical flexure of the midgut and on the age of the patient.

Apart from its musculature, which at times is somewhat thin, the structure of the diverticulum is analogous to that of the intestinal wall, even to the existence of Peyer's patches.

#### HETEROTOPIA

Elements of the gastro-intestinal tract other than mucosa of the small intestine are sometimes present in Meckel's diverticulum. Such elements include gastric and duodenal mucosa and aberrant pancreatic tissue. According to Greenblatt and his co-writers,<sup>6</sup> the presence of heterotopic tissue is estimated as varying from 15 to 25 per cent.

Several theories have been advanced in an attempt to explain the occurrence of this tissue:

Albrecht's theory is based on the pluripotential capacity of the cells lining the omphalomesenteric duct and the primitive intestinal tube to develop into any of the glandular structures in the adult intestine or accessory glands, with the ability to retain one or the other potentiality. This theory would explain the presence of gastric mucosa in Meckel's diverticulum or the occurrence of ectopic pancreatic tissue.

Schaetz's reimplantation or auto-implantation theory reflects an opinion based on experimental observations. He concluded that movements of the maternal organism are communicated to the developing ovum and that fragments of potential gastric mucosa are torn loose and reimplanted at physiologic narrowings in the intestinal tract, one of which is the obliterating omphalomesenteric duct.

Farr and Penke<sup>7</sup> suggested that the vitello-intestinal duct originally may have possessed a digestive function, on the theory that the material in the yolk sac has to be digested. In their series of 13 cases in which operation was performed, gastric mucosa was present in 6 (approximately 50 per cent), while Schaetz found it in only 16 per cent of his autopsy material. These findings, in Farr's opinion, have more than casual significance.

In connection with the foregoing theory, the question has been raised as to whether or not the yolk material really requires digestion in the intraluminal sense, and if so, what type of mucosal epithelium originally lines the yolk stalk. Grosser,<sup>8</sup> in a study of the development

7. Farr, Charles E., and Penke, Madeline: Meckel's Diverticulum, *Ann. Surg.* **101**:1026-1042, 1935.

8. Grosser, O.: Development of Egg Membranes and Placenta, in Keibel, F., and Mall, F.: *Manual of Human Embryology*, Philadelphia, J. B. Lippincott Company, 1910, vol. 1, pp. 173-174.

unhindered entrance and exit of intestinal contents. On the other hand, this wide lumen at its base undoubtedly accounts for the lodgment of a large variety of foreign bodies which have been discovered at operation, prominent among which are pins, seeds, bones, gallstones and intestinal parasites; even a Murphy button previously employed in a patient's gastro-enterostomy was found in his diverticulum three years later.<sup>9</sup> When the opening is narrowed, however, or restricted by a valvelike projection of redundant mucosa—which usually corresponds to an incomplete physiologic atresia—it may cause retention of intestinal contents, fecal stasis or impaction and result in dilatation of the distal end, with inflammation, perforation or intestinal obstruction.

The size of the diverticulum itself may reach such proportions as to produce actual torsion or volvulus of the bowel. This is likely to occur in larger types of diverticula with constricted bases. Mathews<sup>2</sup> reported a diverticulum the size of a hen's egg with a narrow pedicle, causing strangulation of 20 inches (50 cm.) of small intestine by volvulus. In case 21 (fig. 5) of the present series, to be referred to later, a rather large pendulous diverticulum caused partial obstruction by torsion of the segment of ileum to which it was attached.

A diverticulum may occasionally form part of the contents of a hernia (most frequently either inguinal or femoral) and has even been known<sup>3</sup> to have been brought down into the scrotum by descent of the testis to which it was adherent. Another unusual case is that of Brodnax<sup>10</sup> in which a sciatic hernia contained an adherent Meckel's diverticulum, measuring 4 inches (10 cm.) in length. On the whole, however, these cases are unusual. In Wellington's collected series<sup>11</sup> of 326 cases of Meckel's diverticulum (published in 1913), he found only 27 cases which belonged in this category.

The diverticulum may remain adherent to the umbilicus.<sup>12</sup> It is far more dangerous when the part adherent has been reduced to a cord of connective tissue, which, although quite slender, is usually firm and long and a potential source of interference with the intestinal function, either by angulation or torsion of the segment of the bowel or by constriction, causing ileus, intestinal infarction or obstruction. A case of this type was reported by Wellington<sup>11</sup> in which a loop of bowel about 1 foot

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9. Peck, Charles H.: Murphy Button Retained for Three Years in Meckel's Diverticulum: Resection of Ileum; End-to-End Suture, *Ann. Surg.* **49**:134, 1909.

10. Brodnax, John W.: Sciatic Hernia: Report of a Case of Hernia of Meckel's Diverticulum Through the Greater Sciatic Foramen, *J. A. M. A.* **82**: 440-442 (Feb. 9) 1924.

11. Wellington, J. R.: Meckel's Diverticulum with Report of Four Cases, *Surg., Gynec. & Obst.* **16**:74-78, 1913.

12. Cullen, Thomas Stephen: *Embryology, Anatomy and Diseases of the Umbilicus, Together with Diseases of the Urachus*, Philadelphia, W. B. Saunders Company, 1916.

mechanism against the corrosive action of the gastric juice. These ulcers may go on to perforation, with subsequent peritonitis. Johnston and Renner,<sup>16</sup> who recently made a study of 62 previously recorded cases of definite ulcer formation in Meckel's diverticulum, reported perforation in 37 cases (59 per cent).

Neoplastic growths are found occasionally in Meckel's diverticulum. They may be either benign or malignant. According to Liccione,<sup>17</sup> on the basis of an extensive review of the malignant type, reports of only 12 undisputed cases had previously been published. To these he added a case of his own—one of spindle cell sarcoma—making a total of 7 cases of sarcoma, 4 of carcinoid disease and 2 of medullary carcinoma. In addition, there were recorded 3 cases of myxoma of indefinite origin and 3 cases of myxoma of dubious origin.

A granulomatous focus at the umbilicus may be the outward manifestation of an underlying patent or only partially obliterated omphalomesenteric duct. Wellington's study (1913) of 326 collected cases revealed 21 instances of umbilical fistula. These varied from minute openings with slight mucous discharge to those in which the whole intestinal contents were emptied through the umbilicus. Prolapse of the intestine may occur in these cases. Umbilical adenoma has also been found associated with an omphalomesenteric duct.<sup>18</sup>

Less frequently Meckel's diverticulum may be the site of tuberculous or typhoid ulceration and perforation. In the former it is likely to be associated with a similar condition in the intestine. Coley<sup>19</sup> reported an unusual case—the first to be published up to that time (1925)—in which the appendix was simultaneously involved in the tuberculous process. In typhoid, the ulceration or perforation is due to the presence of Peyer's patches in the diverticulum.

#### SYMPTOMATOLOGY

The symptomatology of Meckel's diverticulum is remarkably variable. In a large percentage of cases the anomaly does not give rise to any clinical symptoms whatsoever and is encountered incidentally at operation or at necropsy. On the other hand, when symptoms occur

16. Johnston, Lloyd B., and Renner, George, Jr.: Peptic Ulcer of Meckel's Diverticulum, *Surg., Gynec. & Obst.* **59**:198-209, 1934.

17. Liccione, W. T.: Malignant Tumor of Meckel's Diverticulum, *Am. J. Surg.* **34**:101-103, 1936.

18. (a) Koch, W., in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 4, pt. 1, pp. 175-182. (b) Faust, Louis S., and Walters, Waltman: Fibrosarcoma of a Meckel's Diverticulum Producing Intestinal Hemorrhage, *Minnesota Med.* **14**: 233-236, 1931.

19. Coley, B. L.: Tuberculosis of Meckel's Diverticulum Associated with Tuberculous Appendix, *Arch. Surg.* **11**:519-528 (Oct.) 1925.

approach to more positive diagnosis, especially in those cases in which bleeding occurs, even though the diagnosis may be established by exclusion.

Tarry stools or intestinal hemorrhage should no longer fail to arouse a suspicion of Meckel's diverticulum. Farr and Penke<sup>7</sup> recently reported 4 cases, in all of which the diagnosis was made prior to operation. Persistent bleeding from the diverticulum occurred in all of these instances; in 2, bleeding may have been due to intussusception. The occurrence of bloody stools may also point to the development or the presence of a heterotopic peptic ulcer, and in the adult it may not give rise to any other symptoms. This type of ulcer may closely simulate gastric or duodenal ulcer, from which it may be differentiated roentgenographically. Intestinal hemorrhage and secondary anemia (as in the case of fibrosarcoma reported by Faust and Walters<sup>18b</sup>) may be the only apparent symptoms, even in the presence of a malignant condition. Intestinal bleeding in young children should be differentiated from hemophilia (in which there is a positive family history), purpura hemorrhagica (with the presence of petechiae) and hemorrhagic disease of the new-born.

Intussusception in children under 2 years of age is rarely caused by Meckel's diverticulum. In older children or adults intussusception due to Meckel's diverticulum should suggest itself as a possibility.

It is the inflammatory manifestations of Meckel's diverticulum that are most difficult to diagnose preoperatively. Therefore, at operation, in the absence of an adequate pathologic condition to explain the clinical findings, Meckel's diverticulum should be sought.

Clinically, abdominal pain, vomiting and intestinal bleeding represent the most significant diagnostic criteria of Meckel's diverticulum. From the roentgenologist's point of view, however, a roentgenogram may offer additional diagnostic evidence. Meckel's diverticulum may be pictured in serial roentgenograms of the gastro-intestinal tract. Routine methods, however, may reveal nothing more than a suggestion of the necessity for further detailed examination. An informed roentgenologist directs his attention specifically to study of the small intestine, since the problem requires a different technic and contrast mixture than those employed in routine studies of the esophagus, stomach and colon. A larger quantity of barium sulfate and water, with more frequent observations during the passage of the meal, are requisite. Greater diagnostic accuracy in lesions of the small intestine is possible by this method.

#### PROGNOSIS AND MORTALITY

The prognosis following operation for Meckel's diverticulum, by and large, is favorable. Mathews<sup>3</sup> reported 3 fatalities in his series of 9 cases in which clinical symptoms were evident. Wellington,<sup>11</sup> in his

cecal junction, causing kinking and obstruction of the small intestine. Pathologic examination of the diverticulum showed it to be dark gray, hemorrhagic and necrotic, with a narrow pedicle, and covered by fibrinous exudate. The glandular stroma was infiltrated with lymphocytes, mononuclear cells and occasional polymorphonuclear leukocytes.

CASE 6.—A man aged 36 had severe abdominal pain and had been vomiting for four days. There was slight abdominal distention, with tenderness and rigidity

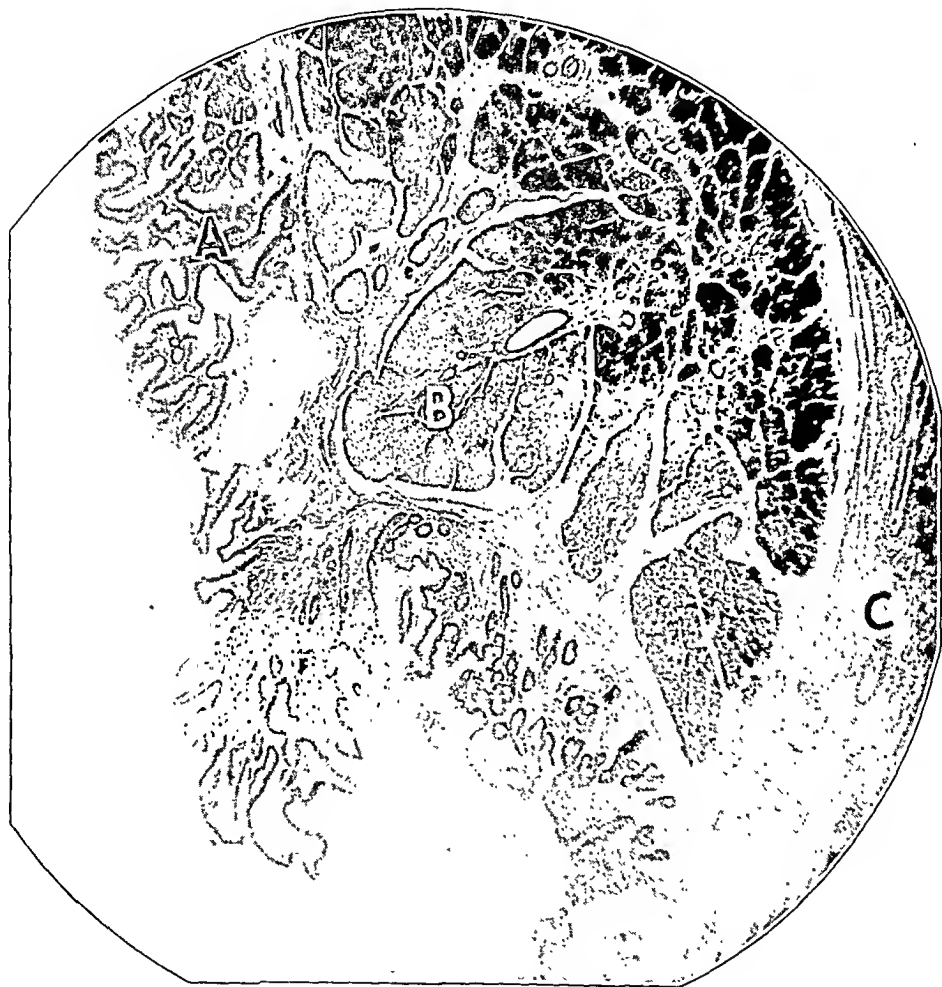


Fig. 1 (case 1).—Photomicrograph of the tip of Meckel's diverticulum. *A* indicates the mucosa, with somewhat tortuous glands; *B*, the accessory pancreatic tissue embedded in submucosa, and *C*, the muscle layer. Medium high power magnification.

in the right lower abdominal quadrant. The white cell count was 9,650, with 65 per cent polymorphonuclears. Operation disclosed a perforated gangrenous appendix, with an abscess, and a diverticulum, 4 inches (10 cm.) long and 15 inches (38 cm.) from the ileocecal junction which showed no pathologic changes. Surgeon's note: "The diverticulum ordinarily would have been removed, but in this case it was deemed unwise in the presence of such a fulminating infection."



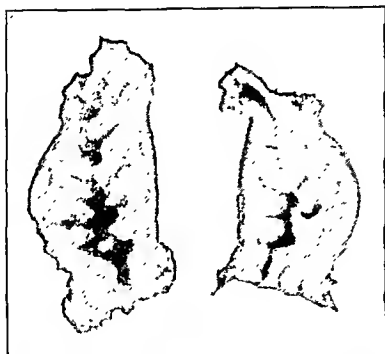


Fig. 3 (case 10).—Meckel's diverticulum with a lining of intestinal mucosa. The lumen shows a bifurcation at the tip.



Fig. 4 (case 10).—Photomicrograph of the tip of the specimen shown in figure 3. *A* indicates the mucosa with well formed glands; *B*, the lymph follicle, and *C*, the muscle layers, both circular and longitudinal. Medium high power magnification.

long and the diameter of the thumb. Pathologic examination of the diverticulum showed marked congestion and edema of the submucosa with an abundance of dilated blood vessels.

CASE 19.—A girl aged 15 years had cramps in the right lower abdominal quadrant and pain in the upper quadrant with nausea, vomiting and anorexia of two days' duration. There were spasm and tenderness in the right lower quadrant. The white cell count was 11,500, with 74 per cent polymorphonuclears. Operation revealed acute appendicitis, a Lane's kink and a diverticulum 3 inches (7 cm.) long with a small mesentery at the base, 18 inches (45 cm.) from the ileocecal junction. Pathologic examination of the diverticulum did not disclose anything remarkable.

CASE 20.—A woman aged 23 had attacks of pain in the right lower abdominal quadrant with nausea and constipation of two years' duration. There was tenderness in the right lower quadrant. Operation disclosed chronic appendicitis and a diverticulum at the mesenteric border of the ileum, 3 feet (90 cm.) from the ileocecal junction. Pathologic examination of the diverticulum did not reveal anything remarkable.

CASE 21.—A woman aged 62 had pain in the epigastric region and the right lower abdominal quadrant of sudden onset, with nausea and diarrhea lasting for two days. There were abdominal rigidity and tenderness in the lower quadrants, most marked to the left and just below the umbilicus. The white cell count was 8,700, with 56 per cent polymorphonuclears. Operation disclosed a small fibrotic appendix which was not considered an adequate cause of the symptoms. Exploration revealed a large pendulous diverticulum, 20 inches from the ileocecal junction and filled with approximately 3 ounces (90 cc.) of serous fluid. The diverticulum had rotated and caused torsion and partial obstruction of a segment of the ileum to which it was attached by a broad base. Pathologic examination of the diverticulum revealed a low grade chronic inflammation, with a moderate number of lymphocytes and plasma cells in the subserosa and muscularis (fig. 5).

CASE 22.—A woman aged 66 had prolapse of the uterus and goiter of fifteen years' duration. Operation disclosed an atrophic uterus and adnexa, an obliterated appendix and a diverticulum. Pathologic examination of the diverticulum did not disclose anything remarkable except for sacculations of the cavity.

CASE 23.—A girl aged 7½ years had repeated attacks of cramplike abdominal pains with vomiting and absence of defecation. The attacks were of three days' duration. Appendectomy had been performed four months previously. Generalized abdominal rigidity and tenderness were present, being more marked just above the umbilicus. The white cell count was 7,600, with 46 per cent polymorphonuclears and 50 per cent lymphocytes. Operation disclosed a diverticulum 22 inches (55 cm.) from the ileocecal junction with the tip of the diverticulum adherent to the cecum at the site of the recent appendectomy; traction by the diverticulum was causing angulation and obstruction of the ileum and gangrene of the intervening segment of the bowel.

#### ANALYSIS OF CASES

This series, a total of 23 cases, represents instances of Meckel's diverticulum found in the course of laparotomies done in the surgical division of the New York Post-Graduate Medical School and Hospital (abdominal operations in other departments not included), as revealed

cases on record at the hospital. Prior to 1930 there were, among others, several instances of intussusception and perforation by a foreign body.<sup>23</sup>

It is interesting to note that although the incidence of males to females is reported in the literature as 4:1, 3:1 and 2:1, and in 1 instance<sup>6</sup> as 2:3, the proportion in the present series is 13:10. The age distribution ranges between 6 months and 66 years.

For the purpose of analysis, the cases in this series have been divided into groups based on surgical and pathologic data (see table), patterned after a workable classification given by Greenblatt, Pund and Chaney.

*Diverticulitis Group.*—In case 3, in which there were perforation of the diverticulum and abscess, autopsy showed chronic adhesive perito-

### *Analysis of Data*

Group of Cases	Number of Cases	Findings	Symptomatology
(a) Diverticulitis group	10 (2 in b)	Acute with gangrene and perforation (cases 3 and 5); acute congestion (cases 2, 9, 10, 12 and 18); chronic inflammation (cases 11, 13 and 21); foreign bodies	Essentially that of appendicitis
(b) Obstructive group	4 (2 in a) (1 in d)	Volvulus (case 21); bands and adhesions (cases 1, 5 and 23); intussusception; contents of hernia	Essentially that of intestinal obstruction
(c) Incidental group	11	Not remarkable pathologically (cases 4, 6, 7, 8, 14, 15, 16, 17, 19, 20 and 22)	Not pronounced
(d) Heterotopic (peptic) group	1 (also in b)	Pancreatic tissue (case 1); gastric mucosa with or without ulceration, hemorrhage, perforation and peritonitis	Mimicry of gastroduodenal ulcer; tarry or bloody stools; perforation
(e) Neoplastic (tumor) group	0	Benign: enterocystoma, adenoma, fibroma, myoma and carcinoid; malignant: carcinoma and sarcoma	Intestinal bleeding; intussusception; obstruction
(f) Umbilical group	0	Adenoma or granulomatous focus; umbilical or fecal fistulas	Referable to umbilicus

nititis involving the lower end of the ileum and the anterior abdominal wall and diffuse bronchopneumonia.

In case 5 gangrene and perforation of the diverticulum caused kinking and obstruction of the small intestine by fibrinoplastic adhesions.

In the remainder of the cases in this group either acute congestion or chronic inflammation of the diverticulum was found.

*Obstructive Group.*—In case 21 a rather large, pendulous and fluid-filled diverticular sac had rotated and caused partial obstruction by torsion of the segment of the ileum from which it arose (fig. 5).

23. An additional case has been encountered at the hospital since the reading of this paper at the New York Academy of Medicine. The patient, who had undergone an appendectomy several years previously, was admitted for the repair of a ventral hernia. During the course of an exploratory examination a diverticulum was found which (as in case 1 of the series herewith presented) contained pancreatic tissue.

the paramedian (rectus) incision, through which more adequate exploration can be made, in preference to the McBurney incision, even though the surgical indication appears to be merely for appendectomy.

Unfortunately it is difficult to obtain adequate data about the more common disturbances of Meckel's diverticulum. In studying the literature one is impressed particularly with the fact that the majority of references are concerned with case reports made interesting by some bizarre type of pathologic process.

The many types of lesions with which Meckel's diverticulum is involved make it one of the gravest mimics of other abdominal conditions. Its significance in routine abdominal operations is therefore quite apparent, and it seems to merit more attention as a purely surgical problem than it has been given.

#### SUMMARY

The embryology and anatomy of Meckel's diverticulum are briefly reviewed.

Heterotopic tissue in Meckel's diverticulum and the various theories of its origin are discussed.

An analysis of a series of 23 case histories is presented on the basis of the pathologic process present and the mechanisms giving rise to abdominal crisis.

The symptomatology and significance of Meckel's diverticulum in routine abdominal operations are stressed, and special emphasis is given to its mimicry of acute abdominal conditions.

Diagnostic criteria of lesions of Meckel's diverticulum are evaluated. Prognosis and mortality rate are included.

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with Howard A. Kelly. He had a patient with a large vesicovaginal fistula which followed irradiation of a carcinoma involving the entire trigonum, the destruction of the tumor obviously resulting in a large opening. The ureters emptied into each side of the fistula, and the bladder prolapsed through the opening into the vagina, presenting at the outlet. Various attempts to hold it up mechanically with pessaries or glass balls failed. Abdominal suspension of the bladder was likewise unsuccessful. I believe that fascia lata could be used to suspend such a bladder to the anterior abdominal wall, as I did in the case of prolapse of the vagina herein reported.

In January 1933, when confronted with a prolapse of the vagina three years after panhysterectomy, I hit upon the idea of suspending the vault with fascia lata. The following report includes a summary of the history and the operative notes:

Mrs. R. P., aged 57, was referred by the late Dr. Fredrick Detrick because of vaginal bleeding of a few days' duration. Dilatation and curettage revealed early adenocarcinoma. On March 27, 1930, bilateral salpingo-oophorectomy, panhysterectomy and appendectomy were performed. After the uterus was removed "one cigaret drain was left in the vagina and the vaginal fornix was closed with chromic catgut sutures; stumps of the round ligaments and infundibulopelvic ligaments were sutured to the fornix of the vagina." The raw surface was covered over by suturing the peritoncum of the bladder "to the posterior vaginal wall." An uneventful recovery ensued, except for a slight low grade infection in the fat abdominal wall.

On July 8, 1931, the patient returned to the office, giving the following history: About five or six weeks before this visit, while spading in the garden, all of a sudden she felt "something give way" and "something came out of her body." Her general health had been good, and she had gained some weight since the operation. She was in excellent general condition, but there was marked prolapse of the vagina, particularly of the anterior wall, on straining, the vault coming down to the outlet (fig. 1). There was no evidence of recurrence of the carcinoma, either on abdominal or on pelvic bimanual palpation. A second degree perineal laceration had been present from childbirth twenty-five years or more before. Apparently two factors had contributed to this prolapse: first, a weakened perineal floor and, second, a severe strain, which tore the vagina away from the suspending round and broad ligaments. A Gehrung pessary inserted as a trial support was unsatisfactory. On one occasion the vagina actually prolapsed through the pessary after a long shopping tour.

The patient was not seen again until Jan. 17, 1933. During the interval there had been continual discomfort. The abdominal scar of the previous operation was well healed. There was definite tenderness about  $3\frac{1}{2}$  inches (8.9 cm.) to the left of the umbilicus, but no masses were made out. The family physician, however, had felt "something loose in the left flank," which he took to be a metastatic abdominal tumor. There was a little resistance over the left lower quadrant at the point of tenderness.

The vaginal outlet admitted two or three fingers; the external genitalia were otherwise normal. Straining brought both walls of the vagina, but especially the anterior wall, down through the outlet. The pelvis was otherwise normal.

(2.5 cm.) below the other end of this same suture. The ends of the suture were anchored in place with black silk. The suture supported the vaginal vault and bladder so securely that a similar suture was placed on the left side, the first part going out under the old broad ligament subperitoneally and around the pelvic wall and anterior abdominal wall to be anchored in the posterior sheath of the rectus muscle. The other end of the suture was brought forward like the one on the right, under the peritoneum of the bladder and through the abdominal wall, just above the symphysis. This gave excellent support to the vaginal vault, the weight of which was equally distributed through these new round ligaments.

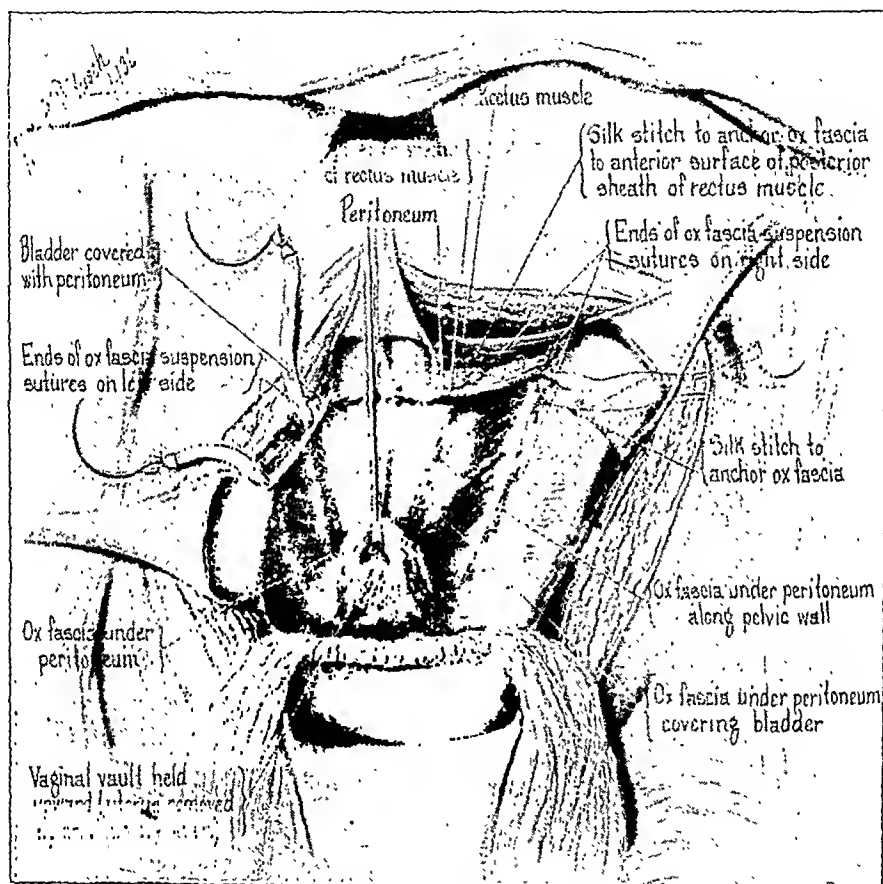


Fig. 2.—The method of placing suspension sutures of ox fascia to draw and hold the vault of the vagina upward.

In placing these sutures, several fundamental principles had to be remembered: This transplanted tissue would not become an integral part of the host unless embedded in a vascular area to allow its reorganization. The fascia could not be left as "guy-ropes" across the peritoneum to catch and kink a loop of bowel. The suture had to be completely hidden. As the fascial suture was rather long, the unused end was worked under the peritoneum of the bladder to give added support to this organ, so that its weight, when full of urine, would not force down the vagina or bring undue strain on the newly made round ligaments. It would have been possible to have buried these sutures by splitting the peritoneum, laying in the

repair the perineum but to determine the necessity of such repair later. The abdominal incision was closed, and the patient left the operating room in good condition.

By February 3, eight days after operation, the patient had made a splendid recovery. All the stitches were out, and the wound had healed nicely. The anterior vaginal wall, which was suspended at operation, held in a perfectly straight line under the base of the bladder. A persisting rectocele was corrected on February 3 by posterior colporrhaphy, local anesthesia being used.

On February 9 the patient was discharged from the hospital to go home and rest in bed for a week or more. Examination on discharge showed that the wound of the second operation had healed nicely. The anterior vaginal wall still held firmly behind the bladder, forming practically a straight line from the urethral orifice to the vaginal vault.

At the last consultation on August 7 it was found that there had been no pelvic disorder, except a mild cystitis about three weeks before. One other attack had followed the first operation in March 1930.

Examination showed the abdomen to be normal. There was a well healed, low midline scar, which was slightly tender at the lower end, but there was no evidence of weakness. The perineum was well lifted and the scar well healed. When the patient strained there was little redundancy of the anterior vaginal wall. The vault was held up in good condition. With one finger in the vagina and the patient straining, no prolapse was noted. The outlet just admitted two fingers, with some discomfort to the patient. The upper portion of the pelvis was perfectly clear. Rectal examination gave negative results.

During the past four years, since the last examination, I have been in touch with the patient off and on and she still remains well. Her physician reported on Feb. 3, 1937, that she had no pelvic symptoms and no cystitis.

#### COMMENT

The problem at hand was the suspension of the vaginal vault which had prolapsed after panhysterectomy through a torn pelvic floor. This prolapse had carried with it the anterior vaginal wall and the posterior wall of the bladder. There was not, however, a large cystocele, indicating that some of the anterior portion of the urogenital diaphragm still held. There were two indications for abdominal section: first, the questionable metastatic nodule (which proved to be a phantom tumor) and, second, suspension of the vaginal vault. When the pelvis was exposed, no round ligaments were found to which to reanchor the vaginal vault. The vagina, which extended less than half way to the symphysis, was far too short to be fixed to the anterior abdominal wall according to the method of Brady<sup>4</sup> or of Thomas,<sup>5</sup> Kocher, Hempel,<sup>6</sup>

4. Brady, Leo: An Operation to Correct Genital Prolapse Following Vaginal Panhysterectomy, *Am. J. Obst. & Gynec.* **32**:295-299 (Aug.) 1936.

5. Thomas, T. Gaillard: Vulvar and Vaginal Enterocoele, *New York M. J.* **42**:705-711 (Dec. 19) 1885.

6. Hempel, E.: Exohysteropexy (Kocher Method) for Prolapse in Elderly Women, *Deutsche med. Wchnschr.* **53**:1382 (Aug. 12) 1927.

The usual types of colporrhaphy often serve to support the bladder and rectum, and the uterus and cervix when present. When the latter two organs are missing, simple colporrhaphy is not always successful. It is then that I would suggest the use of preserved fascia lata.

#### SUMMARY

An operation is described for the suspension of the prolapsed vaginal vault following panhysterectomy, and a case is reported in which successful results have been maintained for four years. The operation consists of the reconstruction of round ligaments out of preserved fascia lata of the ox and the continuation of the newly made ligaments anteriorly under the peritoneum of the bladder to give added support to that organ. It should be pointed out that building new round ligaments is more physiologic than too much mutilation of the vagina. This procedure has been used in only one case, but it is reported in the hope that other surgeons may try this technic to determine its real value.

#### A FORWARD GLANCE

Since strips of fascia supported a prolapsed vaginal vault, would it not be plausible to suppose that similar material would suspend a retroverted or retroflexed uterus? Not uncommonly a heavy uterus has stretched the round ligaments to thin, weak bands. Here would be a splendid place to embed strips of fascia for support.

Is it too far afield to suggest the use of Koontz' preserved fascia lata in other forms of vaginal and perineal repair, especially when the pelvic fascia has been stretched out so thin as to be of little support, often there being little more than bladder or rectal and vaginal wall from which to rebuild a good pelvic floor? In such cases it might be well to weave strips of fascia back and forth or to use a large flat piece to fill in the defect—as emphasized by Koontz.<sup>3</sup> Fothergill<sup>13</sup> emphasized in 1926 what the anatomists Elliott Smith, Cameron and Derry had pointed out:

That the uterus, vagina and bladder are not so much suspended from above or propped up from below as they are attached by their sides where they receive their blood supply, and held in normal position by subperitoneal tissue which intervenes between the organs and the more fixed lateral structures in the pelvic floor.

Koontz' preserved fascia, either as strips or in one large piece, anchored to the lateral pelvic structures, certainly restores normal physiologic support.

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13. Fothergill, W. E.: *The Development of Vaginal Operations for Genital Prolapse*, Brit. M. J. 1:273-274 (Feb. 13) 1926.



proliferation of fibroblasts and endothelial cells with many foreign body giant cells. Sections of tissue from the monkeys showed extensive mechanical rupture and necrosis of muscle fibers. In places there were numerous multinucleated regenerating muscle buds and single myocytes. Wolfe used rats and injected the same solution six times daily into the abdominal muscles. Microscopic examination showed a distinct proliferation of fibroblasts, but no mention was made of any other tissue changes. Bratrud, using dogs and rabbits, injected a solution composed of phenol, alcohol and Lloyd's specific tincture of thuja; in addition, he used solutions of tannic acid in strengths from 0.5 to 5 per cent and also Piña Mestre's solution. He injected 1 cc. of the solutions weekly for six weeks before examining the tissues. Microscopic study showed a marked proliferation of fibroblasts dipping down between muscle fibers. There was no infiltration of polymorphonuclear cells or any evidence of necrosis, except in the tissue of rabbits into which Piña Mestre's solution was injected, as noted by Hall. No giant cells were found. Fibrosis was more marked with the solution of tannic acid than with the solution containing thuja. Injection into the peritoneum caused no abscess formation but produced marked proliferation of fibrous tissue so as to obliterate the peritoneum completely. Rice, experimenting with dogs, first used the Bratrud solution but soon discarded it because when used in doses larger than from 4 to 5 minims (0.2 to 0.3 cm.) tissue necrosis was produced. He then used sodium psyllate (sylasol) and cut sections at intervals of fifteen hours and five, eight, fourteen, eighteen and forty-two days after injection. In sections obtained fifteen hours after injection he noted an exudative reaction of polymorphonuclear leukocytes with few fixed connective tissue cells and some necrosis of the muscle, and subsequent sections showed a gradually changing fibroblastic reaction of fibroblasts into a mature fibrous tissue in from eighteen to forty-two days.

Since so limited an amount of comparative experimental work has been done, it is difficult to evaluate the actual results of the injection treatment of hernia and the value of the different solutions so widely recommended. It seems obviously important to know what histologic changes occur and what type of repair follows at various intervals.

In this experimental study four solutions, namely, galtanol, sodium psyllate, Bratrud's solution and a modification of Mayer's solution, which have been strongly advocated and used with good clinical results, and Carabba's solution and a solution of iodine and tannic acid were used in order to compare their histologic effects.

The injection method of treating hernia was first used about a hundred years ago. Velpeau<sup>9</sup> in 1835 used injections of a solution of

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9. Velpeau, A. A. L. M., cited by Marcy, H. O.: *The Anatomy and Surgical Treatment of Hernia*, New York, D. Appleton & Co., 1892, p. 272.

## EXPLANATION OF FIGURE 1

Fig. 1.—*A*, section of tissue obtained twenty-four hours after the injection of galtanol. This section shows slight edema with a marked cellular reaction in the subcutaneous area and between the muscle bundles. The cells are chiefly polymorphonuclear leukocytes, although some lymphocytes and large mononuclear cells can be made out. A few fibroblasts are also present. The upper area shows a ruptured blood vessel. *B*, section of tissue obtained seven days after the injection of galtanol. This section shows marked proliferation of fibroblasts extending deeply between the muscle bundles. The fibroblasts are assuming a parallel formation, being separated by young fibrous tissue. The fibroblasts are large and stain deeply. Many new capillaries can be seen throughout the section. Several lymphocytes and wandering cells are scattered throughout the section, but no polymorphonuclears are present. *C*, section of tissue obtained two weeks after the injection of galtanol. This section shows a much denser area of proliferating connective tissue extending between muscle bundles. The fibroblasts are more elongated and are arranged in parallel layers separated by more deeply staining strands of fibrous connective tissue. Many multinucleated giant cells are present; there are also a few lymphocytes. *D*, section of tissue obtained eight weeks after the injection of galtanol. This section shows a more mature fibrous tissue adjacent to muscle substance in which many multinucleated giant cells are still present. These are filled with brownish granules. *E*, section of tissue obtained eight weeks after the injection of galtanol. This is another area of section *D*, which shows a dense mature fibrous tissue firmly adherent to the muscle substance and dipping in between the muscle bundles to a slight extent.

dangerous to inject the sclerosing solution into it because of the chemical peritonitis that would result. In a great number of cases in which operative treatment would be hazardous because of age, physical defects or repeated operative recurrences, this method would be of great value.

In order to obtain good results, the sclerosing solution should be one that (1) causes no pain, (2) is not injurious to the tissues, (3) does not produce a systemic reaction, (4) produces a minimum of inflammatory reaction with a marked proliferative phase, (5) produces marked fibrosis to fill up the defect with firm scar tissue and (6) does not produce peritoneal inflammation if inadvertently injected into the peritoneal cavity. With these points in mind and in view of the absence of any recorded comparative study, the experiment was undertaken to compare the relative merits of each solution to be tested.

#### EXPERIMENTAL PROCEDURE

Adult rats were used. On each side of the ventral abdominal wall a sclerosing solution was injected subcutaneously in an attempt to have the point of the needle reach the abdominal muscles. The amount of the substances varied from 3 to 8 minims (0.18 to 0.5 cm.). The following solutions were used:

##### Galtanol

A hydro-alcoholic tincture of selected botanic extracts of gallic and tannic acid

##### Sodium psylliate (sylasol)

A 5 per cent solution of a vegetable oil extracted from the seed of the psyllium groups

##### Bratrud's solution

Phenol .....	50 parts
Alcohol .....	25 parts
Lloyd's specific tincture of thuja.....	25 parts

##### Modification of Mayer's solution

Zinc sulfate .....	4.0 cc.
Phenol .....	24.0 cc.
Glycerin .....	15.0 cc.
Aqueous solution of butyn (0.1%).....	100.0 cc.

##### Tannic Acid and Iodine Solution

Tannic acid .....	1.3 Gm.
Iodine .....	4.0 cc.
Alcohol .....	30.0 cc.
Double-distilled water .....	60.0 cc.

##### Carabba's solution

Phenol .....	45.0 cc.
Sodium borate .....	1.04 Gm.
Salicylic acid .....	1.04 Gm.
Glycerin .....	120.0 cc.
Spirit of camphor.....	240.0 cc.

## EXPLANATION OF FIGURE 3

Fig. 3.—*A*, section of tissue obtained twenty-four hours after the injection of Bratrud's solution. This section shows slight edema of the muscle bundles with a polymorphonuclear leukocytic reaction. In the inflammatory exudate there are also several histiocytes and a few fibroblasts. There is slight necrosis of muscle cells. *B*, section of tissue obtained seven days after the injection of Bratrud's solution. This section shows a marked fibroblastic reaction extending into the muscle tissue. The fibroblasts are elongated and are held together by strands of fibrous tissue. There are many newly formed blood vessels throughout, several lymphocyte and wandering leukocytes. *C*, section of tissue obtained two weeks after the injection of Bratrud's solution. This section shows fibrous tissue between the muscle bundles. It is denser than that in section *B*, and the fibroblasts are much smaller and thinned out. There are many lymphocytes, wandering leukocytes and also several multinucleated giant cells. *D*, section of tissue obtained three weeks after the injection of Bratrud's solution. There are coarse bundles of fibrous tissue adjacent to the muscle that appears more mature than those in section *C*. No giant cells or other cells are noted. *E*, section of tissue obtained eight weeks after the injections of Bratrud's solution. This section shows an adult dense fibrous tissue. The nuclei of the fibroblasts are very small and widely separated by the collagenous tissue.

## EXPLANATION OF FIGURE 4

Fig. 4.—*A*, section of tissue obtained twenty-four hours after the injection of iodine and tannic acid solution. This section shows a fibrinous exudate in which there are many polymorphonuclear leukocytes. In the lower part of the section is an abscess. Throughout are lymphocytes, fibroblasts and a few large mononuclear cells. *B*, section of tissue obtained three days after the injection of iodine and tannic acid solution. This section shows a proliferation of great numbers of fibroblasts in the fibrinous plastic exudate. There are many endothelial and transitional leukocytes present as well as some lymphocytes. A few polymorphonuclears are still to be seen. *C*, section of tissue obtained seven days after the injection of iodine and tannic acid solution. This section shows a more adult fibrous tissue in which the fibroblasts are smaller and fewer in number. There are several new blood vessels throughout. Few lymphocytes are present. *D*, section of tissue obtained two weeks after the injection of iodine and tannic acid solution. This section shows a more mature fibrous tissue in which the nuclei are much smaller and faintly staining. The tissue appears to be composed of coarse strands of fibrous tissue closely bound together. There are many lymphocytes and wandering leukocytes throughout the new fibrous tissue. *E*, section of tissue obtained eight weeks after the injection of iodine and tannic acid solution. This section (high power magnification) shows an adult dense fibrous tissue in which the nuclei are small and compressed into spindle shapes.

## EXPLANATION OF FIGURE 5

Fig. 5.—*A*, section of tissue obtained twenty-four hours after the injection of Carabba's solution. This section shows a marked exudative reaction in the subcutaneous area and extending between the muscle bundles. In the fibrinous exudate there are many polymorphonuclear leukocytes, fibroblasts, several endothelial leukocytes and also a few lymphocytes. *B*, section of tissue obtained seven days after the injection of Carabba's solution. This section shows a marked proliferation of fibroblasts extending into the muscle tissue. The intercellular substance is loose and faintly staining. There are many multinucleated giant cells present throughout the section. *C*, section of tissue obtained two weeks after the injection of Carabba's solution. This section shows a more mature fibrous tissue adjacent to the muscle section. The nuclei are compressed and held together by coarse fibrous strands. *D*, section of tissue obtained four weeks after the injection of Carabba's solution. This section shows coarse bundles of fibrous tissue adjacent to muscle, which are more mature than those in section *C*. *E*, section of tissue obtained eight weeks after the injection of Carabba's solution. A dense firm adult fibrous tissue is present.

The animals were killed at intervals of one hour, twenty-four hours, three days, seven days, two weeks, three weeks, four weeks, six weeks and eight weeks, and sections obtained from the sites of injection were studied. In addition, four rats were given injections intraperitoneally of galtanol, sodium psylliate, a solution of iodine and tannic acid and Carabba's solution, and sections were made in forty-eight hours to note the peritoneal reaction and the effect on the abdominal contents.

Tissue from the sites of the injection was excised, fixed in formaldehyde, embedded in paraffin, cut in longitudinal sections and stained with hematoxylin and eosin for microscopic study, and in addition some sections were stained with the triple Mallory stain, the silver method of Foot and Foot and the Van Gieson stain for the connective tissue reaction.

### RESULTS

Because the reactions induced by each sclerosing solution were so nearly similar, I have grouped the typical reactions at the different time intervals and noted the individual variations. A complete analysis of reactions to each solution is given in tables 1 to 6. In table 7 is presented a summation of the histologic changes with all the solutions.

Sections obtained one hour after injection showed a slight cellular reaction of polymorphonuclear leukocytes, a few lymphocytes and histiocytes and occasional fibroblasts. The tissue into which the modification of Mayer's solution was injected showed severe necrosis of the muscle.

Sections obtained twenty-four hours after injection showed slight edema of the injured area with marked exudation of polymorphonuclear leukocytes. A few lymphocytes and histiocytes and a moderate number of fibroblasts were present. The tissue into which the modification of Mayer's solution was injected showed the maximum amount of necrosis of the muscle, and in that into which the iodine and tannic acid solution was injected there was a small abscess, which did not contain any microorganisms.

Sections obtained three days after injection showed that the proliferation of fibroblasts was predominant, with many wandering phagocytes and some lymphocytes. There were few polymorphonuclear cells. Necrosis of the muscle was still most evident in the tissue into which the modification of Mayer's solution was injected.

Sections obtained seven days after injection showed early fibrosis with all solutions. The fibroblasts were much denser, and fibrils could be made out between them. Many histiocytes and a few lymphocytes were present. Only the tissue into which Carabba's solution was injected showed a few multinucleated giant cells.

Sections obtained two weeks after injection had coarser and denser fibrous tissue separating the more mature fibroblasts. Many wandering phagocytes were still present, and in the tissue into which galtanol and the modification of Mayer's solution were injected there were many multinucleated giant cells.

which the modification of Mayer's solution was injected showed many giant cells.

Sections obtained six weeks after injection showed fibroblastic tissue similar to that seen in the sections obtained at four weeks. Tissue into which galtanol was injected still showed many foreign body giant cells filled with brownish granules.

TABLE 5.—*Histologic Changes Produced by Tannic Acid Solution*

	1 Hr.	24 Hr.	3 Days	7 Days	2 Wk.	3 Wk.	4 Wk.	6 Wk.	8 Wk.
Necrosis.....	+	0	+	0	0	0	0	0	0
Lymphocytes.....	++	++	0	+	++	0	+	0	0
Leukocytes.....	++	++++	++	0	0	0	0	0	0
Histiocytes.....	+	+	++	0	+	+	++	0	0
Fibroblasts.....	0	++	++	+++	++++	+++	+++	++	0
Giant cells.....	0	0	0	0	0	0	0	0	0
Fibrosis.....	0	0	0	++	++	+++	+++	+++	++++

TABLE 6.—*Histologic Changes Produced by Carabba's Solution*

	1 Hr.	24 Hr.	3 Days	7 Days	2 Wk.	3 Wk.	4 Wk.	6 Wk.	8 Wk.
Necrosis.....	++	+	++	++	+	0	0	0	0
Lymphocytes.....	+	+	++	0	0	0	0	0	0
Leukocytes.....	+	+++	0	0	0	0	0	0	0
Histiocytes.....	+	++	++	++	0	+	0	0	0
Fibroblasts.....	0	++	+++	+++	+++	0	+	0	0
Giant cells.....	0	0	0	+++	0	0	0	0	0
Fibrosis.....	0	0	+	+	+++	+++	+++	++++	++++

TABLE 7.—*Summation of Histologic Changes Produced by Sclerosing Solutions*

	Necrosis	Acute Inflam- mation	Early Repair	Late Repair	Fibrosis	Fibro- blastic Reaction
Galtanol.....	+	+++	++	+++	++++	++
	3 days	1 day	3-7 days	2-3 wk.	3-8 wk.	2-8 wk.
Sodium psyllate.....	+	+++	+++	++++	++++	0
	3 wk.	1 day	3-7 days	2-4 wk.	1-8 wk.	
Bratrud's solution.....	+	+++	++++	++++	++++	±
	3 wk.	1 day	3-7 days	1-4 wk.	1-8 wk.	2 wk.
Modification of Mayer's solution	+++	++	++	+++	++++	+++++
	3 days	1 day	3-7 days	2-4 wk.	2-3 wk.	4 wk.
Tannic acid solution.....	+	++++	++	+++	++++	0
	3 days	1-3 days	3-7 days	2-4 wk.	1-8 wk.	
Carabba's solution.....	++	+++	+++	+++	++++	+
	2 wk.	1 day	3-7 days	1-2 wk.	2-8 wk.	1 wk.

Sections obtained eight weeks after injection all showed a dense fibrous tissue, except the tissue into which galtanol was injected, which still had many giant cells in one area.

The sections stained with the silver method of Foot and Foot showed many fine argyrophilic fibers in the reticulum among the collagen fibers at the seven day period, which were gradually and completely replaced by dense collagen at the eight week period.



The results in this experimental work obtained with the aforementioned sclerosing solutions well demonstrate these tissue changes. All solutions except the iodine and tannic acid solution elicited a mild inflammatory exudative reaction up to twenty-four hours with a marked subsidence at the three day period. With the iodine and tannic acid solution an abscess was evident at the twenty-four hour period. The reaction to all the solutions at the end of the seven day interval consisted chiefly of a proliferation of fibroblasts with early repair. At later periods, from two to eight weeks, the young fibroblasts could be seen undergoing changes of maturity, becoming smaller and more elongated, and the argyrophilic reticulum fibrils between them were condensed and supplanted by firm collagenous tissue. The modification of Mayer's solution was the only solution to produce marked necrosis of muscle up to three days, while the necrosis of muscle produced by Carabba's solution was moderate up to seven days. The foreign body reaction to galtanol persisted for from two to eight weeks. This indicates the failure of the tissues to get rid of the residual irritant solution, and while it may continue the proliferation of connective tissue, a possible danger lies in the formation of a foreign body granuloma.

It has not as yet been determined which constituents of each solution have a stimulating effect on the proliferation of new connective tissue. This problem is under consideration and will ascertain the rationale for using the various ingredients of each solution.

#### SUMMARY

In a series of rats sclerosing solutions were injected into the muscles of the anterior abdominal wall on each side. Six different solutions were used: (1) galtanol, (2) sodium psylliate, (3) Bratrud's solution, (4) a modification of Mayer's solution, (5) iodine and tannic acid solution and (6) Carabba's solution. Biopsy specimens were obtained from the sites of injection at intervals of one hour, twenty-four hours, three days, seven days, two weeks, three weeks, four weeks, six weeks and eight weeks. Intraperitoneal injections were made with galtanol, sodium psylliate, iodine and tannic acid solution and Carabba's solutions, and the animals were examined in forty-eight hours.

There was a slight necrosis of muscle, except when modification of Mayer's solution was used, and then it was marked. The inflammatory exudation was mild, reaching its peak at twenty-four hours and then subsiding completely in the next forty-eight hours. Iodine and tannic acid solution was the only one to produce abscess formation at the end of the twenty-four hour interval. Proliferation of fibroblasts became predominant at three days, and at seven days there was some evidence of new collagenous tissue with dense fibrous tissue at eight

## PERITONITIS

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### ANATOMY AND HISTOLOGY

The peritoneum is the largest serous membrane in the body. Hertzler<sup>1</sup> measured the peritoneal and the cutaneous surfaces of twenty cadavers and found that the average of the measurements for the former was 3,268 square inches and for the latter, 3,436 square inches. Thus the opinion usually held that the surface area of the peritoneum is about equivalent to the cutaneous surface area of the body is approximately correct.

A part of the peritoneum is applied to the abdominal wall, the remainder being reflected over the viscera contained in the peritoneal cavity. In the male the peritoneum is a closed sac, but in the female the free ends of the fallopian tubes open directly into the peritoneal cavity. The surface of the peritoneum is covered with flattened cells which are variously called epithelium, endothelium or mesothelium. According to Jordan,<sup>2</sup> these cells are mesothelium. They are sometimes known as squamous epithelium. Maximow refers to the cell layer covering the surface of all serous membranes as mesothelium. However, reference to the superficial cells of these serous membranes as endothelium is usual in clinical descriptions and will be adhered to here.

The endothelial cells of the peritoneum have undulating margins, the corners being frequently pushed between the sides of adjoining cells. This irregularity may be accentuated by contraction or by successive contraction and expansion, particularly on the under-surface of the diaphragm. The endothelium of the peritoneum differs in its form from the endothelium lining the blood and lymph vessels, the latter being usually arranged with the long axis of its cells parallel with the axis of the vessel, and the cells are elliptoid in shape and more irregular in outline and in size than the peritoneal cells. The cells of the peritoneum are quite flat and have ovoid nuclei. In staining, they may group themselves in such a manner as to suggest stomas or stigmas.

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The DaCosta Foundation Oration, read before the Philadelphia County Medical Society, Philadelphia, April 14, 1937.

1. Hertzler, A. E.: *The Peritoneum*, St. Louis, C. V. Mosby Company, 1919, vol. 1.

2. Jordan, H. E.: *A Text Book of Histology*, New York, D. Appleton-Century Company, Inc., 1934.

act somewhat as a pump and mechanically force exudate into the peritoneum more rapidly than it would be absorbed without such alternate compression and relaxation.

Beneath the layer of endothelial cells is a basement membrane, made up of connective tissue fibrils arranged in parallel bundles and bound together with a cement substance. The cement substance appears not only to hold the connective tissue fibrils of the basement membrane together but to keep the endothelial cells in place much as tiles would be held by cement beneath them. In irritation of the peritoneum an excessive amount of cement substance is apparently one of the first products of peritoneal exudation, as it emitted between the cells and presents a fibrinous discharge.

Beneath this basement membrane is a layer of loose connective tissue, through which course blood and lymph vessels. In regions where the peritoneum is less mobile than others, as over the bands of the colon, the central tendon of the diaphragm and over the liver and spleen, there is a small amount of connective tissue. The connective tissue in other regions, such as the parietal peritoneum, is more abundant and frequently contains much fat.

The blood vessels of the peritoneum may be divided into those that can be seen under normal conditions and those that are not visible. The latter are doubtless abundant not only in the peritoneum but in other tissues of the body and are called by Hertzler potential vessels. Ordinarily these small vessels do not contain red blood cells and are invisible. They probably transport serum, and possibly some white blood cells may make their way through them. In the presence of irritation they quickly dilate and become active with circulating blood. It is these vessels that under the sudden stimulus of irritation or inflammation provide the diffuse redness of the peritoneum. They can be demonstrated experimentally by the injection of a solution of silver nitrate and appear under the microscope to divide the peritoneum into quadrilateral areas. They arise at right angles from the visible vessels. They are separated from the endothelial cells only by their lining and a basement membrane.

The lymphatics of the peritoneum lie in the same stratum of connective tissue in which the blood vessels are found, only probably somewhat deeper. They form a network of relatively large vessels, irregular in size. The large lymph channels are connected by fine canals, but there seems to be no organic connection with the blood vessels or with the connective tissue spaces. The lymph channels are apparently a closed system, just as the blood vessels are, and interchange with the connective tissue spaces is doubtless a chemical process and does not involve an actual mechanical connection with the special spaces. Lymph vessels

anywhere. When these particles are located, plastic exudation throws up a granular mass, and they are often encapsulated. This requires two or three hours and may result in a permanent resting place of the foreign particles in the peritoneum somewhat similar to what is observed with granules of soot in the lungs or powder stains in the skin. Some of the particles gain access to the lymph nodes. The number of cells in the peritoneal fluid is increased, the cells coming from the points of greatest irritation in the peritoneum. These cells form a new peritoneum around the capsules of the foreign bodies when they are surrounded by the cells. At first polymorphonuclears predominate, but later mononuclears take part in this process. Phagocytic cells may surround the small particles and carry them to the lymph nodes, or they may, according to Hertzler,<sup>3</sup> break up the foreign body, destroying themselves at the same time. However, if the particles are soluble, such as particles of fibrin, the cells usually remain alive. Very small particles of lampblack introduced into the peritoneal cavity are doubtless disposed of in part by being carried into the circulating blood, and the larger particles are surrounded by a cell or cells and may be carried to the lymph nodes or encapsulated.

Defibrinated blood is rapidly absorbed from the peritoneum, but coagulated or whole blood is absorbed much more slowly. According to Jordan,<sup>4</sup> Shipley and Cunningham<sup>5</sup> and others, the chief agents in disposing of clots are the monocytes (macrophages), which carry the debris both to the blood and to the lymph capillaries of the peritoneum. Bacteria are disposed of in the same manner.

Absorption is hastened by many things, among others by massage. The action of the diaphragm tends to promote absorption from the peritoneum in the upper part of the abdominal cavity. Slowing of absorption may be caused by abundant fibrinous exudate, especially in walled-off cavities.

The increase in intra-abdominal pressure hastens absorption from the peritoneum so long as the increase is not sufficient to retard the returning flow of blood. After this point the increased pressure tends to delay absorption.

The omentum usually has an active function in inflammation of the peritoneum. Its protective influence in attempting to wall off inflam-

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4. Jordan, H. E.: Personal communication to the author. Jordan, H. E., and Speidel, C. C.: Studies on Lymphocytes: I. Effect of Splenectomy, Experimental Hemorrhage and a Haemolytic Toxin in the Frog, *Am. J. Anat.* **32**:155 (Sept.) 1923; The Behavior of the Leukocytes During Coincident Regeneration and Thyroid-Induced Metamorphosis in the Frog Larva, with a Consideration of Growth Factors, *J. Exper. Med.* **40**:1 (July) 1924.

5. Shipley, P. G., and Cunningham, R. S.: Studies on Absorption from the Serous Cavities, *Anat. Rec.* **2**:181, 1916.

in secondary repair. More highly differentiated repair usually follows primary repair, but the first bond in holding the injured tissues together, aside from temporary agglutination by exudate, is connective tissue.

In some excellent experimental work, Hertzler<sup>3</sup> seems to have shown that in the healing of peritoneal wounds under optimum conditions without bacterial infection, unusual trauma or the presence of blood clots, a clear structureless exudate is thrown down a few minutes after the peritoneal surfaces are approximated with fine silk sutures. Within ten minutes bundles of fibrin extend from one surface of the peritoneum to the other, and within a few hours the bundles are fully developed. Usually there is a subperitoneal edema, which elevates the serous surfaces and brings them closer together. The bundles of fibrin contract as they mature. These primary bundles of fibrin remain in position under aseptic conditions and gradually form *directly* fibrous tissue without any replacement. These changes begin about the third or fourth day, and by the sixth or eighth day the bundles of fibrin are *directly* converted into adult connective tissue bundles. Cells may invade the interstices between the bundles, but they do not replace them. These bridges of fibrin connective tissue are covered with endothelium, not from the adjacent margins of the endothelium, according to Hertzler, but with endothelium formed from monocytes, wandering cells or clasmotocytes which spread over the surface and flatten out. In this way there is complete endothelization in a week or ten days. This favorable process, however, may be interrupted by sepsis, by undue trauma of the tissues or by digestive juices on the peritoneal surface. Constitutional conditions, such as intense jaundice, may also affect such healing.

The muscular and mucous layers of the apposed bowel require several weeks for healing, but the important surgical feature is the prompt union of the peritoneal surfaces. If conditions are not satisfactory for primary healing, secondary union may occur. Here there is agglutination of the surfaces from a granular mass of exudate, which sooner or later is absorbed. This exudate consists of granular débris with exudate from the peritoneal surfaces. Granulation tissue is formed and then come fibroblasts, from which connective tissue develops.

Aseptic irritation of the peritoneal cavity may cause adhesions, which may be temporary or permanent. With infection, there is an outflow of serum which infiltrates the connective tissue spaces and forms exudate on the surfaces where the tissues are infiltrated with leukocytes. Hyperemia occurs with leukocytic infiltration of the connective tissue around the blood vessels, and then there is migration of the omentum to the site of infection, probably by some cellular mass attraction similar to chemotaxis. The surfaces of the organs are covered with exudate

there is intestinal obstruction. In inflammation, however, the diffuse redness, which has been mentioned as an early stage caused by dilatation of the potential vessels, is always a distinct feature, though dilated vessels without this diffuse redness may occur around the margin of the peritonitis or may be an accompaniment of some other condition, such as obstruction. The hyperemic stage of peritonitis occurs early, within the first hour after perforation of a duodenal ulcer, for instance. The distal loops of bowel may show only dilatation of normal or service vessels, whereas those nearest the site of a perforation will have the diffuse redness. The abdominal wall usually shares in these vascular changes, hyperemia of the parietal peritoneum taking place. Even when the hyperemia is slight, there may be a loss of the glistening surface of the normal peritoneum. When hyperemia is marked, there is an escape of red cells outside of the blood vessels which causes dark areas within the peritoneal surface, even when there is no exudate. This shows an intense irritation.

The exudative stage is a rapid sequel to the hyperemic stage. Serum and cells are found about the walls of the blood vessels in the subperitoneal tissue and on the surface of the peritoneum. This exudate is probably protective and forms adhesions to the adjacent structures, so that the inflammatory process will not extend into the general peritoneal cavity. The peritoneum is always thickened with edema, which elevates it. In the exudative stage the appearance of the peritoneum is significant. If the exudate is pink or reddish, it shows a formation of a granulation fibrin and good defense; if it is whitish and smooth, it indicates that fibrin and protective adhesions are not being formed, and the prognosis is grave. The adherent tissues here are easily separated, and infection will break down the feeble barriers. As the disease progresses, there may be numerous areas which are walled off.

In the plastic stage the exudate forms adhesions and joins the peritoneal surfaces together, so walling in the affected area and protecting the peritoneal cavity. The surfaces of the peritoneum are fused together by this material in the exudative stage. If these areas are separated, a sheetlike exudate is found which is made up of granular fibrin and remains attached to the peritoneal surface. Occasionally the exudate covers wide areas. The exudate sometimes becomes vascularized as true granulation tissue. This is chiefly found when the peritoneal surface is long exposed or when there is prolonged contact with a drain, especially a gauze drain. The plastic exudate may be without structure and whitish or grayish. This shows a lack of reaction and is ominous. It is the type of exudate usually found at necropsy.

These changes do not necessarily succeed each other in the order named. Hyperemia occurs first; then exudation occurs, and plastic

## SYMPTOMS OF ACUTE PERITONITIS

When acute peritonitis is spoken of it is usually a type of septic peritonitis that springs from lesions of the gastro-intestinal tract.

The symptoms of acute peritonitis may vary considerably. In a typical case pain is the first symptom. This may be due to spasm or to exudation into a viscus together with hyperemia, which permits the transmission of pain from the sympathetic nerves. The methods of transmitting pain from the peritoneal cavity have undergone considerable discussion and cannot be dealt with here at length. Years ago Lennander claimed that the viscera of the peritoneal cavity were devoid of any sensation. It seems to be proved now, however, that the sympathetic system can transmit certain types of pain, and this can be excited largely by tension within the tissue or by spasmodic contraction of the muscle. Soon after this occurs, however, the parietal peritoneum becomes affected, and the pain is then transmitted by cerebrospinal nerves. The pain usually originates from the sympathetic nerves, being transmitted to the ganglions, and is often complained of first in the epigastrium, but in a few hours it occurs at the site of the lesion. The pain caused by established peritonitis is transmitted by the cerebrospinal nerves. It is increased by the movement of inflamed surfaces on each other, so that pressure on the abdomen which brings the inflamed surfaces together increases the pain and tenderness. After adhesions have occurred, the pain is frequently lessened, because the inflamed parts are somewhat splinted together by adhesions. Muscular rigidity is one of the early symptoms of peritonitis and is doubtless a reflex, such as is described by Hilton<sup>12</sup> in "Rest and Pain" to protect the inflamed surface by the splintlike action of the muscles. It is most pronounced at the site of the greatest irritation and is dependent on the cerebrospinal reflex. The rupture of a hollow viscus, such as the stomach or bowel, is usually accompanied by intense abdominal pain and muscular rigidity. Often there is marked shock, soon followed by elevation of temperature and a rapid pulse.

Inflammation of a viscus that is limited to the viscus and does not involve the parietal peritoneum may not be accompanied by muscular rigidity. This occurs in certain instances in which an inflamed appendix, for instance, is in the pelvis attached to a mobile cecum and not in close proximity to the parietal peritoneum. The muscular rigidity may be lessened when the infection is walled in or the inflammation of the parietal peritoneum diminishes. As the disease advances, however, and the patient becomes more toxic, there may be some lessening of the muscular rigidity, even though the disease is progressing.

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12. Hilton, J.: *Rest and Pain*, edited by W. H. A. Jacobson, New York, W. Wood & Co., 1879.

leakage is slow, there usually is not the pronounced classic symptom of intense pain and muscular spasm that ordinarily follows perforation of a viscus.

In the elderly person with a low resistance, the white blood count may appear to be normal. Usually there is a shift to the left of the polymorphonuclears, but even this may be comparatively insignificant. In children, too, the symptoms are often irregular.

#### ETIOLOGY OF SPREADING PERITONITIS

In regard to the etiology of spreading or general peritonitis, an interesting article by Pflaum<sup>13</sup> on "A Postmortem Analysis as to Etiology in One Thousand Cases of Peritonitis" gives much information. This report is based on 1,000 cases of peritonitis found at 14,263 necropsies in the department of pathology of the University of Minnesota from 1920 to 1932. Of these 1,000 cases, 52.5 per cent were in males, though peritonitis is supposed to be more common in the female. There were 221 cases (22.1 per cent) of postoperative peritonitis. This does not include cases in which operation was performed when peritonitis was already present, such as cases of gangrenous appendicitis or of ruptured ulcer. Resection for carcinoma was responsible for most of the postoperative deaths. There were 10 cases of peritonitis which developed after paracentesis for ascites and 126 cases (12.6 per cent) due to acute appendicitis, in some of which peritonitis developed after operation. One hundred cases (10 per cent) were due to tuberculosis and 27 (7.7 per cent) to infection from abortion. There were 45 cases (4.5 per cent) of peritonitis of primary or undetermined origin. Peritonitis occurred in 13 cases (1.3 per cent) of strangulated hernia, in 10 cases (1 per cent) of typhoid, in 6 cases (0.6 per cent) of septic sore throat, in 7 cases (0.7 per cent) of erysipelas, in 2 cases (0.2 per cent) of phlegmonous gastritis and in 2 cases (0.2 per cent) of bacterial endocarditis.

The incidence of peritonitis after operations is interesting, as is also the rather high incidence of tuberculosis of the peritoneum. The fatal cases of peritonitis resulting from perforation of a peptic ulcer numbered 48 (4.8 per cent). The ages of these patients ranged from 12 to 81 years. In 16 cases the perforated ulcer was in the stomach; 10 of these cases occurred in males and 6 in females, the ages averaging from 18 to 76 years. In 45 cases (4.5 per cent) no local or distant focus of infection could be demonstrated. One third of the patients in this group were under 1 year of age, but the ages of the remainder ranged

13. Pflaum, C. C.: A Postmortem Analysis as to Etiology in One Thousand Cases of Peritonitis, *Am. J. Clin. Path.* 5:131 (March) 1935.



foration of any other viscus. The type of bile peritonitis, however, which may be considered as producing different symptoms is that in which uncontaminated bile escapes. This may follow a wound of the gallbladder or, more frequently, operations on the common duct or the gallbladder in which bile escapes.

In drainage of the common duct, which is a frequent procedure after the duct is opened for the removal of stones, bile usually escapes around the drainage tube, but adhesions quickly form and conduct it to the surface, though there may be some obstruction along the drainage tract which forces the bile into the peritoneal cavity. Instances in which the gallbladder is removed and the abdominal wall closed without drainage and bile escapes may be due to faulty ligation of the stump of the cystic duct, to a wound in some accessory ducts which were not observed at operation or to injury to the common duct. It is in such cases that true uncomplicated bile peritonitis occurs. This bile does not appear to have a very irritating effect at first, but if it escapes in large quantities or if the pressure is not relieved, the bile insinuates itself about the diaphragm, and death may occur. If the bile is mixed with pancreatic or gastric juice, as in perforation of the duodenum, the infection is much more violent. If the perforation permits the free escape of duodenal contents, death from shock may occur in a few hours.

In some interesting work on bile peritonitis by Moon and Morgan,<sup>17</sup> it was found that the intraperitoneal injection of sterile bile into animals produced a severe illness, frequently characterized by symptoms of shock. Death in coma resulted in twenty-four hours. The death seemed to be characteristic of shock. Moon and Morgan found that intravenous injections of sterile normal dog bile produced symptoms similar to those which followed injection into the peritoneal cavity. Their conclusions were:

Intraperitoneal or intravenous injections of bile or of sodium glycocholate produce the shock syndrome characteristically in dogs. This is accompanied by hemoconcentration as in shock otherwise produced. Sublethal degrees of shock follow sublethal doses of the agents mentioned. These may recover or may result in pulmonary edema, pneumonia and subsequent death. The postmortem findings are the same as those following shock otherwise produced. These are: marked capillary and venous engorgement of the lungs, serosa, gastro-intestinal mucosa, liver and kidneys; edema of lungs, gastro-intestinal mucosa, and serous effusions; anemia of the splenic substance. The evidence indicates that bile or its salts cause acute injury to the walls of capillaries and venules. This results in atony and increased permeability, whereby a disparity develops between blood volume and volume-capacity of the vascular system. Such a disparity manifests itself in the shock syndrome.

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17. Moon, Virgil H., and Morgan, David R.: Shock in Bile Peritonitis, *Proc. Soc. Exper. Biol. & Med.* **34**:743 (June) 1936.

eight or seventy-two hours and then sterilized in an autoclave and injected into the peritoneal cavity in the uncontaminated state, death resulted within a few hours from shock and peritonitis, and no bacteria could be recovered. This reaction was doubtless due to some toxic product that formed during the period of incubation, before the bacteria were killed. Neither the sterile liver nor sterile bile salts, according to Trusler and his co-workers, seemed to cause an infection of the peritoneal cavity by any bacteria.

In a further communication, Trusler and Martin<sup>21</sup> made some interesting observations. They found that when 70 Gm. of parenchymal elements of fresh liver was injected intraperitoneally they were essentially harmless. When as much as 50 Gm. of blood vessel, bile ducts and connective tissue of the liver was injected, the animal died. Animals given intraperitoneal injections of the epithelial cellular elements of the liver appear able to sterilize this material, while animals receiving the other portions of liver tissue died with bacterial growth in the peritoneal cavity.

These observations show the importance of removing the necrotic or devitalized liver tissue in cases of intra-abdominal trauma in which the liver is involved.

*Pneumococcic Peritonitis.*—Pneumococcic peritonitis is comparatively rare, but it appears to be a clinical entity. It was first described in 1865 by Bozzolo, when he reported a case occurring in Turin. Since then groups of cases have appeared in the literature from time to time. The disease appears more frequently in Germany and in France than in America. The infection may arise from one of four ways: from the blood stream in cases of disease of the respiratory tract, such as pharyngitis, bronchitis or pneumonia; by penetration from the diaphragm in cases of disease of the lung; by penetration from the wall of the bowel in cases of pneumococcic infection of the intestine, and through the uterus and fallopian tubes in cases of infection of the vagina. All of these routes have some advocates, but the two most probable sources of infection are from the blood stream in cases of infection of the lungs, trachea or pharynx and through the vagina. The last route was strongly advocated by McCartney and Fraser<sup>22</sup> in 1922. They cited an interesting group of cases in which pneumococcic peritonitis occurred in female infants and children. McCartney expressed the belief that pneumococcic peritonitis is frequently due to

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21. Trusler, Harold M., and Martin, H. E.: The Cause of Death in Liver Peritonitis, *Surgery* 1:243 (Feb.) 1937.

22. McCartney, J. E., and Fraser, J.: Pneumococcal Peritonitis, *Brit. J. Surg.* 9:479 (April) 1922. McCartney, J. E.: Pathogenesis of Primary Pneumococcal Peritonitis, *J. Path. & Bact.* 26:507 (Oct.) 1923.

tion usually does not occur until the third or fourth day of the disease. The tenderness, sometimes beginning in the lower right quadrant, is more likely to be diffuse. A feature that has been noted in this disease by many writers is the prominence of the umbilicus. If the early days of the acute stage can be weathered and the patient begins to improve, the exudate often localizes about the navel, and if the patient is not operated on, the pus may actually break through the navel.

A positive blood culture is obtainable in about half of the cases, but not until the second or third day of the disease. The leukocyte count is usually high, frequently as high as 40,000, though in rare instances it may be normal.

It is necessary to make a differential diagnosis between appendicitis and pneumococcic peritonitis. If the diagnosis cannot be reasonably determined otherwise, aspiration of the abdomen with a spinal puncture needle should be done and a drop or two of the peritoneal exudate should be withdrawn and examined as a smear. If numerous organisms are present with a predominance of colon bacilli, peritonitis of an appendical origin may be considered highly probable, but if only a single organism is present the peritonitis is probably not of appendical origin. Short-chain streptococci alone sometimes may be difficult to distinguish from pneumococci, but even so peritonitis due to these organisms will probably not have its origin in the appendix. If gram-positive diplococci or pneumococci are present, the diagnosis of pneumococcic peritonitis is confirmed.

The exudate at first is a thin, cloudy, yellowish free fluid with many flakes of fibrin. This accumulates in large quantities. After a few days it thickens and becomes a pure pus, usually retaining a greenish tinge but with many large masses of fibrin. Perforation at the umbilicus, which has been mentioned, may take place whether the pus is encapsulated or not. Occasionally there may be large abscesses in the pelvis.

The peculiar features about this type of peritonitis are its tendency to occur in female infants or children, the frequent accompaniment of diarrhea, the high leukocyte count which is usually present, the absence of intense muscular spasm and the tendency for the fluid to accumulate around the umbilicus.

The treatment seems to be medical, at least in the early stages. Operation in the first stage probably does more harm than good. Whatever may be the source of the infection, its original focus, unlike appendical peritonitis, cannot be removed, and there seems to be no point in draining a small area while the disease is progressing elsewhere. After the pus has localized, however, operation, consisting of a simple incision and the insertion of a small drain, is indicated. Not infrequently there may be several points of localization which must be drained.

many cases. It is well known that the gonococcus does not stand a high temperature, and heat seems to be peculiarly suitable for the treatment of this disease.

Patients with gonococcic peritonitis and salpingitis should not be operated on as a rule. Even after the disease has subsided, salpingitis may be cured with the applications of heat through the vagina and the general principles of rest. If a collection of pus appears in the cul-de-sac, it may be opened by vaginal puncture, but disturbing the fibrinous exudate in the cul-de-sac without definite localization of pus may make matters worse. Owing to the nature of the infecting organism, this type of peritonitis is radically different from the peritonitis caused by infection from the gastro-intestinal tract, as from the appendix.

*Tuberculous Peritonitis.*—Tuberculosis of the peritoneum may be found at any age, though most frequently before the twentieth year. In middle life or later, tuberculous peritonitis is usually a terminal stage of a process that has existed for many years. Tuberculous peritonitis may be divided into two forms: the primary form in which no other focus of the disease is present and the secondary form in which a focus can be demonstrated elsewhere.

The primary form is probably rare, because a small focus that might have furnished the original source of tuberculosis of the peritoneum may have healed.

In the secondary form the primary focus may be difficult to detect. The bacteria are borne by the blood stream, as not infrequently occurred when it was the practice to operate on cervical tuberculous lymph nodes.

Diffuse tuberculous peritonitis is probably caused by infection of the blood stream from some primary focus of tuberculosis elsewhere. Tuberculous peritonitis is, of course, different from the localized tuberculosis of the abdominal viscera, such as in the ileocecal region and the fallopian tubes, which are occasionally the site of a primary tuberculosis. In the ileocecal region tuberculosis of the bowel may assume a form in which there is great thickening and infiltration of the cecum and the terminal portion of the ileum with large tumor formation. In this type there is much plastic exudate, and the disease involves the entire wall of the bowel, though not infrequently the mucosa seems intact. The peritoneum over this region is secondarily affected, and usually the infection is localized.

Tuberculosis of the peritoneum is often found in delicate children, though it may occur in children who are apparently in good health.

When the disease does occasionally begin from the superficial parts of the ileocecal region or the fallopian tubes, the onset may be acute, with chills, high temperature, abdominal pain and slow distention, some-

disease, or it is possible to have a gradual change from one form into the other. Usually fully developed connective tissue is not formed from this fibrin, though this may occur and adhesions of connective tissue show part of the healing process. As the healing progresses, however, the adhesions commonly loosen and are absorbed. The fibrinous activities may continue in the subperitoneal tissue with great thickening of the walls of the peritoneum. In such instances the tissue is so thickened that the gross appearance of tuberculosis will be lost, and the peritoneum will resemble parietal pleura in cases of advanced tuberculosis of the lung.

The caseous type results when there is marked thickening, and exudation and degeneration occur. The process is the same here as in tuberculosis elsewhere. The toxic material liquefies the tissue, and ulceration may result. When ulceration occurs, the exudate becomes granular and agglutinates the adjoining coils of the intestine, thus protecting the surrounding region against perforation. The spaces between the loops of intestine in such a type of tuberculous peritonitis may be filled with caseous contents, and histologic examination discloses the typical appearance of the tubercle. In the acute form there may be no tubercles easily demonstrated, but microscopic examination may show the tubercle bacilli. Giant cells are not necessarily indicative of tubercles. Not infrequently in chronic irritation of the peritoneum particles of fibrin are encapsulated and giant cells form around them.

The treatment of tuberculous peritonitis depends somewhat on the type of the disease. However, under all conditions the general treatment for tuberculosis should be instituted. Rest, with the administration of as much nutritious food as can be retained, fresh air, proper direction of the diet and the avoidance of chilling of the body are as essential in tuberculosis of the peritoneum as in tuberculosis elsewhere. Exposure to sunshine and heliotherapy are often helpful but should be given cautiously. Much harm may be done by excessive or improperly directed light treatment.

The treatment of the disease in the exudative stage, in which there is abundant ascitic fluid, has been the subject of much controversy and discussion in former years. There were strong advocates of various operative technics, many of which seemed to be successful in the early stages. They varied from an abdominal incision and exposure of the patient so that sunlight would fall into the abdomen for a short while to incision and drainage, manipulation of the intestines and dusting with various kinds of powder. Patients not infrequently recovered after any one of these treatments. It is now known, however, that all of these technics probably produced hyperemia of the intestines, and it was the hyperemia, whether it was caused by removal of ascitic fluid,

form of peritonitis is the septic form which has its source in the gastro-intestinal tract, and preventive treatment and therapy to be used after the disease has developed demand fuller consideration. As will be seen from the reference to the table by Pflaum,<sup>13</sup> in which he reports the results of necropsy in 1,000 cases of peritonitis, the most common cause of death was peritonitis developing after operation. This does not include cases in which peritonitis existed at the time of operation, such as instances of appendical peritonitis or of peritonitis due to rupture of a peptic ulcer. It is surprising that 22 per cent of all the deaths were due to peritonitis arising after operation.

I shall first consider local peritonitis. By local peritonitis is usually meant the type caused by aseptic irritation of the peritoneum, such as is found accompanying acute cholecystitis. This forms an exudate, and not infrequently the gallbladder becomes adherent to the surrounding tissue. The viability of the gallbladder is high, and in most cases the inflammation subsides and the bacteria do not penetrate the wall of the gallbladder. However, in some instances the gallbladder may become gangrenous and rupture. This converts an aseptic local peritonitis into a septic local peritonitis, which may extend, depending much on the resistance of the tissues and the nature of the infection.

Local peritonitis from the appendix is different because of the uncertain vascularity of the appendix and its proneness to rupture or become gangrenous and the fact, too, that its contents are usually far more virulent than the contents of the gallbladder. While, then, it frequently is wise to treat local peritonitis such as develops around the gallbladder expectantly because of the tendency of the inflammation in the gallbladder to resolve, local peritonitis around an inflamed appendix is another problem and should usually be treated by removing the focus of infection, the appendix.

The general principles of the treatment of spreading peritonitis may be stated as the removal of the focus of infection, if possible, the institution of drainage, the provision of rest to the gastro-intestinal tract and the administration of a sufficient amount of water, electrolytes and calories intravenously in order to give this rest. There are exceptions to some of these recommendations, such as in cases of general or spreading peritonitis in which the focus of infection cannot be definitely determined and in cases of so-called idiopathic or primary peritonitis, which may result from hematogenous infection by streptococci or possibly from small emboli carried in the blood stream that may produce minute permeable foci in the gastro-intestinal tract. In such instances drainage with continual pouring out of septic material into the peritoneal cavity from an irremovable focus will do little good. Drainage accompanied

In the matter of direct preparation for the prevention of peritonitis, numerous substances have been injected into the peritoneal cavity before operation, with the purpose of establishing relative local immunity. They have included various strengths of dextrose solution and other materials, but the two best known preparations have been amniotic fluid extract, which has been sponsored by Young, Johnson and Marks, and vaccine products with the colon bacillus as a base.

The preparation of amniotic extract was used by Johnson, his first report being made in 1927.<sup>25</sup> Young and Marks<sup>26</sup> reported a series of 49 clinical cases, many of them involving operations on the large intestine. The exact type of operation, however, is not given. In these 49 cases there were 3 deaths, 1 apparently being from pneumonia without peritonitis, and the other 2 from peritonitis.

Rankin and Barga<sup>27</sup> developed a vaccine made from colon bacilli and streptococci. Some surgeons have injected various solutions of dextrose into the peritoneal cavity a few days before operation.

The purpose of administering these substances is not to effect a true vaccination in the sense of obtaining general constitutional immunity but to increase the local resistance of the peritoneum by bringing about a heavy influx of phagocytes, chiefly the polymorphonuclears. The value of these so-called vaccines has not been definitely determined, though apparently they have not justified the high hopes that were felt for them at one time. Thus, Rankin,<sup>28</sup> who once believed that the mortality rate from peritonitis subsequent to operations on the large bowel was materially reduced by the use of the vaccine which he and Barga developed, recently stated that he had abandoned the use of the vaccine and secured equally good results without it.

Steinberg,<sup>29</sup> in reporting on the use of amniotic fluid experimentally, stated that it apparently had no beneficial effect in preventing peritonitis

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25. Johnson, H. L.: Observations on the Prevention of Postoperative Peritonitis and Abdominal Adhesions, *Surg., Gynec. & Obst.* **45**:612 (Nov.) 1927; An Exposition of the Preparation and Administration of Amniotic Fluid Concentrate, *New England J. Med.* **212**:557 (March 28) 1935.

26. Young, Edward L., Jr., and Marks, G. A.: Pre-Operative Preparation of the Peritoneum in Surgery of the Large Intestine, *Surg., Gynec. & Obst.* **59**:610 (Oct.) 1934.

27. Rankin, F. W., and Barga, J. A.: Carcinoma of the Colon: Intraperitoneal Vaccination by Mixed Vaccine of Colon Bacilli and Streptococci, *Arch. Surg.* **19**:906 (Nov.) 1929. Rankin, F. W.: Vaccination Against Peritonitis in Surgery of the Colon: Further Report, *ibid.* **22**:98 (Jan.) 1931.

28. Rankin, F. W.: Resection of the Rectum and Rectosigmoid by Single or Graded Procedures, *Tr. Am. S. A.* **54**:155, 1936; *Ann. Surg.* **104**:628 (Oct.) 1936.

29. (a) Steinberg, B.: The Experimental Background and the Clinical Application of the *Escherichia Coli* and Gum Tragacanth Mixture (Coli-Bactragen) in Prevention of Peritonitis, *Am. J. Clin. Path.* **6**:253 (May) 1936. (b) Steinberg, B., and Goldblatt, H.: Protection of the Peritoneum Against Infection, *Surg., Gynec. & Obst.* **57**:15 (July) 1933.

Aleuronat is a diabetetic flour and seems to stimulate the formation of the leukocytes in the bone marrow. The action of the tragacanth appears to be largely in retarding the absorption of the bactragen. Ordinarily when a solution of soluble toxins and dead bacteria is placed in the peritoneal cavity it is quickly absorbed and the influence is ephemeral, but the tragacanth prevents this quick absorption and spreads the influence of the colibactragen over a period of at least several days. That the colibactragen acts in this manner and not constitutionally is shown by Steinberg<sup>29a</sup> in a patient in whom the fat of the abdomen was so great that the colibactragen was accidentally injected into the deep layers of the abdominal wall instead of into the peritoneal cavity. No reaction followed. However, when this mistake was realized, a peritoneal injection was made and the usual reaction occurred.

Strains of colon bacilli have been found by Steinberg<sup>29</sup> to be more effective in bringing out the leukocytes than any other bacteria. This preparation is not specific for colon bacilli but affects streptococci found in cases of peritonitis which originate in the gastro-intestinal tract. This is shown by the engulfing of the various bacteria by the phagocytes. The experiments apparently do not clarify the role that the humoral antibodies may play, but they do not show any evidence that they play an important part.

When this colibactragen is introduced, the phagocytosis attacks the bacteria irrespective of the species of bacteria and is usually complete in from four to eight hours. The presence of the large number of polymorphonuclears in the peritoneal exudate, the free bacteria and the observation of the leukocytes that contain ingested bacteria in the protected dogs contrasted with the small amount of leukocytes in the control dogs seem to indicate the manner in which this colibactragen works. When it is used, the bacteria appear to remain almost entirely in the peritoneal cavity, where they are consumed by the phagocytes, but without it they escape from the peritoneal cavity rather rapidly. In dogs with experimental peritonitis that are protected by this colibactragen the leukocytes are apparently diminished in number in the first hour, but in the second and third hours they are markedly increased, whereas in the nonprotected animals there is a consistently low number of leukocytes.

It must be emphasized that this protection is not specific against a single organism but is effective against a mixed bacterial infection and that phagocytosis is accomplished before the production of the toxic soluble substances by the bacteria and that these soluble toxic substances are responsible for death from peritonitis. The essential purpose of this colibactragen is to allow the slow passage of the leukocyte-stimu-



If it can be determined that the peritonitis is caused solely or chiefly by a hemolytic streptococcus, treatment with sulfanilamide should benefit. Large quantities of fluid should be given, not by mouth or by rectum but by the intravenous administration of 5 per cent dextrose in Ringer's solution, so providing physiologic rest for the gastrointestinal tract. Five per cent dextrose in distilled water is indicated if it seems that there is an undue accumulation of salt. Stronger solutions of dextrose, such as 10 per cent, may be administered for a short time, but they tend to irritate the vein, and the 5 per cent solution is isotonic.

On general principles, the source of the infection should be eliminated if possible. Thus, in perforation by a peptic ulcer or a typhoid ulcer, it is essential to close the perforation. This should be done as simply as possible. In cases of peptic ulcer there seems to be no need to cauterize the ulcer or to do any extensive operation. If the ulcer is in the duodenum the perforation may be closed by a series of mattress sutures placed transversely along the margin of the ulcer and tied gently, so they will not pull out, and this is reinforced by one or two other rows of sutures. The last sutures bring over peritoneal covered fat or omentum.

The treatment of the distention and the adynamic ileus that accompany peritonitis is important. The introduction into the stomach of a Jutte or Levine tube, which was first advocated by Matas,<sup>31</sup> who also first advised the continuous intravenous injection of a 5 per cent solution of dextrose, is indicated. Recently this has been developed and elaborated by Wangensteen<sup>32</sup> and others and is now in general use.

As a precautionary measure in almost every operation on the abdomen which is prolonged or which involves the stomach or intestine, a Jutte tube should be inserted until the patient can take food. This may be connected with a suction apparatus, as developed by Wangensteen.

The administration of morphine is helpful in cases of peritonitis. Attention was called to this by Plant and Miller<sup>33</sup> and by Gruber and

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31. Matas, Rudolph: Continued Intravenous "Drip," with Remarks on the Value of Continued Gastric Drainage and Irrigation by Nasal Intubation with Gastroduodenal Tube (Jutte) in Surgical Practice, *Ann. Surg.* **79**:643 (May) 1924.

32. Wangensteen, O. H.: Therapeutic Considerations in Management of Acute Intestinal Obstruction: Technic of Enterostomy and Further Account of Decompression by Employment of Suction Siphonage by Nasal Catheter, *Arch. Surg.* **26**:933 (June) 1933.

33. Plant, O. H., and Miller, G. H.: Effects of Morphine and Some Other Opium Alkaloids on the Muscular Activity of the Alimentary Canal, *J. Pharmacol. & Exper. Therap.* **27**:361 (June) 1926.

more harm than good will result, and it would be best to trust to nature to wall off and limit the peritonitis until an abscess has formed. It must be recalled that in the early stages of peritonitis the eventual result is established, and, while the patient may not die immediately, if the peritonitis is poorly handled fatal errors will have been committed from which there can be no recourse.

The general principles of treating acute appendicitis should be those that apply in other perforations of the intestinal tract. They may be stated briefly as follows:

1. Operate at any stage as soon as the diagnosis is made.
2. Make a McBurney incision, through which the appendix may be approached and drainage, if necessary, established.
3. Always remove the appendix.
4. Use suction to remove pus or exudate; do not place gauze within the peritoneal cavity, and on no condition sponge away the pus or the exudate.
5. Treat the stump of the appendix simply, by merely tying it and disinfecting it. Do not bury the stump.
6. Give the bowel rest by refraining from proctoclysis and enemas at all times and by supplying the water, electrolytes and calories by intravenous continuous injection of 5 per cent dextrose in Ranger's solution.

These principles are self-evident. Unless they are followed through collectively, however, they should not be attempted, for they are dependent on each other. For instance, there is no point in attempting to remove an appendix from fibrinous exudate if at the same time the bowel is to be packed off with gauze and the pus sponged away with gauze. Each time the pus is sponged away, bacteria are forced by the sponge into the tissues. It is practically the same as if the septic material were actually injected into the tissues. If a suction apparatus is not available, at any rate the pus or liquid exudate should not be sponged; it might be drawn off with a syringe. The necessity of giving the bowel a rest is also obvious. It is a truth laid down by Hilton in "Rest and Pain" that is one of the classic foundations of treatment, and if the inflamed bowel is to be given exercise in absorption or motion by the introduction of water through proctoclysis or nutrition or purgatives through the mouth, this well established principle is being violated. While it is necessary to supply water, electrolytes and, to some extent, calories, this can be readily done intravenously with the proper precautions by means of the continuous direct flow, without the drip apparatus. The dangers from thrombosis are increased by too concentrated a solution and by the use of the drip apparatus which may permit aspiration

not include cases in which the appendix was removed incidentally during another operation but only cases in which the operation was done solely or chiefly for appendicitis. The results are shown in table 2.

Of the 3 deaths from acute appendicitis, 1 resulted from a pulmonary embolus in a man aged 59 who had a gangrenous appendix. He recovered and was about to leave the hospital, when he was suddenly stricken with a pulmonary embolus and died in a few minutes. Another death was that of a very obese man who suffered from chronic alcoholism with a bad liver and kidneys. The appendix was removed. Paralytic ileus and uremia developed, and the patient died the sixth postoperative day. Necropsy showed no peritonitis. The third death was that of a patient who had acute appendicitis and also an abscess of the tube on the left side which involved the ileum. The appendix was removed. The abscess and part of the ileum had to be resected. Five days after operation the patient died from intestinal obstruction and localized peritonitis on the left side.

Abscess and localized peritonitis were the cause of death of a man 72 years of age who had a retrocecal appendical abscess. During convalescence he had pulmonary edema and cardiac weakness, from which he died four days after the operation.

The fifth death was in a neglected case of generalized peritonitis in which there was gangrenous bowel which had to be resected in the presence of infection.

In none of the fatal cases was there uncomplicated appendical spreading peritonitis.

a small tumor for about eleven months. It was our custom then to cut into the tumor and decide on its pathological nature from the naked-eye appearance of the tissue. This tumor was not encapsulated and not cystic, but distinctly circumscribed and buried in a senile breast. The moment we cut into and pressed on it, there exuded from its surface many grayish-white, granular cylinders, which I called at that time comedos. From the gross appearance the tumor was diagnosed as malignant, and the radical operation was performed. The nodes were not involved, the breast was senile, and there was no gross or microscopic evidence of chronic cystic mastitis. The patient lived nineteen years after operation, dying at the age of eighty-six.

Since then I have been recording such cases and have divided them into two groups—pure comedo-adenocarcinoma and comedo-adenocarcinoma with areas of fully developed cancer of the breast. Examples of the latter group, in which areas of pure comedo are present in an otherwise fully developed cancer of the breast, are the more frequent, and for this reason the operator must always bear in mind the possibility of cancer when comedos are present in a tumor. Hence, if the tumor is too large to exclude the presence of malignant areas by frozen section, a radical mastectomy should be done.

In an inaugural dissertation entitled "Carcinoma Intracaniculare Proliferans Mammarum," Selling<sup>3</sup> described the histologic changes in a tumor of the breast which had been surgically removed. Unfortunately the clinical history could not be obtained. The specimen measured 7 cm. in length, 4 cm. in width and 3 cm. in thickness. The growth was of a papillary nature, which was distinctly demonstrated when water was allowed to flow over the tumor. The tissue spaces contained many nests of tumor cells, and the blood vessels were apparently involved. The histologic characteristics of this tumor are quite different from those of the duct carcinoma described later, and the probabilities are that in the case described by Selling the growth originated in the acini and the ducts were secondarily involved. The title of the dissertation would seem to accentuate the proliferating potentialities of the growth which led to extensive invasion of the lymphatic spaces.

Dietrich and Frangenheim<sup>4</sup> stated:

It has not been determined whether the carcinoma with intracanicular extension originates in the epithelium of the ducts (Jacobaeus). Early cases of this type are not known, and in advanced stages it is not possible to decide the relationship between the epithelium of the ducts and the carcinoma. Comparison with carcinomas of other organs does not permit one to conclude that there is a definite relationship between the duct epithelium and the carcinoma, although it apparently has been demonstrated conclusively in cases of Paget's disease.

The character of the cells of carcinoma growing in the ducts is the same as that of the cells of carcinoma solidum, but there is frequently a tendency to flattening

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3. Selling, T.: *Carcinoma Intracaniculare Proliferans Mammarum*, Inaug. Dissert., Würzburg, P. Scheiner, 1898.

4. Dietrich, A., and Frangenheim, P.: *Die Erkrankungen der Brustdrüse*, in von Bruns, P.: *Neue deutsche Chirurgie*, Stuttgart, Ferdinand Enke, 1926, vol. 35, p. 171.

of a normal breast, although they may be irregular in shape and arrangement. (2) The tumour has only one stalk. (3) The epithelial contents of the tumour may undergo cystiphorous desquamative changes similar to those that can be observed in otherwise normal breasts. . . . (4) This new breast formation may undergo carcinomatous changes and form a distinct type of duct carcinoma. At this point it is interesting to recall the fact that in benign, multiradicular papillomata, formation of ducts and acini can often be discovered.

This description applies to papillary carcinoma of the ducts rather than to the type of duct carcinoma described in this paper.

The duct carcinoma about to be described, we believe, represents a distinct type which frequently can be recognized clinically. In discussing duct carcinoma it must be remembered that in the development of the ducts there are two distinct phases of differentiation, and in the development of the acini, still another phase. The relation of adenocarcinoma to the terminal part of the tubules and acini is generally recognized. The origin of the carcinoma described by Paget from the germinal epithelium of the nipple and that of the primary ducts seems to be well established. The clinical and pathologic pictures of carcinoma arising from the epithelium of the branching mammary ducts between the nipple, the terminal portion of the ducts and the acini, however, have remained ill defined.

#### CLINICAL DESCRIPTION

Comedo carcinoma usually presents two rather characteristic pictures. Before discussing these, a few case histories will be given which will illustrate the clinical picture of the diffuse form.

CASE 1.—A. B., a Negress aged 63, had had two children. The menopause occurred at the age of 52. Seven years before admission to the hospital she discovered a small lump in the breast somewhat removed from the nipple and about the size of a pigeon's egg. She experienced pain from time to time and rubbed the lump with camphor liniment. After five and one-half years the tumor became as large as a hen's egg. Hot applications were then used. Two months before the patient's entrance to the hospital a yellowish discharge from the nipple was noticed. The skin covering the breast took on a pigskin appearance.

When the patient was examined, the right breast was found to be as large as a grapefruit and somewhat lobulated, but a single tumor could not be palpated. The overlying skin in areas appeared thinned, and small nodules could be palpated in it. A distinct pigskin appearance was noted (fig. 1). The breast was not fixed to the chest. No enlarged nodes were palpable in the right axilla. The enlarged breast was lobulated, and apparently a tumor which had an elastic feel occupied the anterior half. Because of these findings, a diagnosis of intracanalicular myxoma was made in spite of the lymphedema. A radical operation was performed on Feb. 23, 1934. When the tumor was incised, the cut surface had the appearance of a two by four which had been sawed across (fig. 2). Many epithelial plugs could be expressed from the cut surface. Suppurative phlebitis of the cephalic vein developed, and the patient died on March 10.

As has been stated, this diffuse comedo carcinoma presented some of the clinical features peculiar to intracanalicular myxoma.

CASE 2.—M. F., a white woman aged 34, noticed a lump in her breast eight months after childbirth. This breast had not produced milk. When examined, the patient stated that the tumor had been noted for four and one-half years. She had been pregnant a year before this examination was made. Four months before the examination pain developed in the breast. The breast then became red, and a discharge from the nipple was noted. The nipple became retracted, and the tumor increased rapidly in size. The patient's mother and her mother's mother both died of carcinoma of the breast. Both breasts were large, but the left was nearly twice the size of the right. The tumor was the size of a grapefruit, and was firm, lobulated and adherent in places to the skin. There were no palpable axillary nodes. A radical operation was performed on March 4, 1917. According to the operative note, no enlarged nodes were found. The pectoral muscles were not invaded. The patient was well and free from recurrences in 1936, nearly twenty years after the operation. Many dilated spaces were found on gross examination, and from these were discharged a yellowish fluid which resembled condensed milk. Histologically the tumor was a comedo carcinoma.

CASE 3.—L. S., a white woman aged 53, had had three children. The menopause occurred at the age of 42. One month before the present examination she felt a burning sensation in her left breast. She touched the area and found a tumor. She did not believe that the growth had increased much in size. On examination a mass about 7 cm. in diameter and without definite margins was found to the outside of the left nipple. The overlying skin was slightly dimpled. There were no palpable lymph nodes in the axilla. The complete operation for cancer was done on Nov. 14, 1932, following a biopsy. Plugs of solid material could be expressed from dilated ducts in the gross specimen. The microscopic diagnosis was comedo carcinoma. Examination of the lymph nodes for cancer gave negative results. The patient was seen on Dec. 5, 1935, at which time the roentgenograms of the spine and lungs did not show any evidence of metastases. A recent inquiry concerning the patient's present condition has not been answered.

CASE 4.—B., a white woman aged 48, had had seven children, whom she nursed. Since nursing her last child, three and one-half years before the present examination, she had noted a hardness of the right breast with crusting of the nipple, apparently due to a chronic discharge. On examination a hard mass which involved the entire upper half of the breast was palpated and some dimpling of the overlying skin was noted. A few drops of serosanguineous discharge was expressed from the right nipple. No enlarged lymph nodes could be palpated in either axilla. A radical operation was performed on Aug. 31, 1927. The gross specimen had the typical appearance of a comedo carcinoma. Plugs were expressed from the ducts. The diagnosis was confirmed by microscopic examination. Metastases were found in the midaxillary nodes but there were none in the nodes at the apex or base of the axilla. The patient died of metastases five years after operation.

The four cases have been reported to give the clinical picture of the diffuse comedo carcinoma. It is a slowly growing tumor which involves the greater part of the affected breast, and an isolated tumor cannot be palpated in the enlargement. Despite the size of the growth there are frequently no palpable lymph nodes. Small elevations in the skin may

two years' duration, and in six it had been noted for five years or more. The location of the comedo carcinoma suggests an origin in the larger ducts. It often develops near the nipple at the margin of the areola, in many cases just above and to the outside of the nipple (fig. 3). Symptoms referable to the nipple are common. A watery, milky or yellowish discharge is noted not infrequently. Retraction or fixation of the nipple occurs often, and occasionally the patient complains of burning and itching of the nipple, a symptom more common in Paget's disease. In one case the nipple was destroyed as a result of ulceration. In a few cases a serosanguineous discharge from the nipple was noted.

The tumor is usually located near the skin, and atrophy of the overlying fat and dimpling of the skin occur. Redness of the skin is

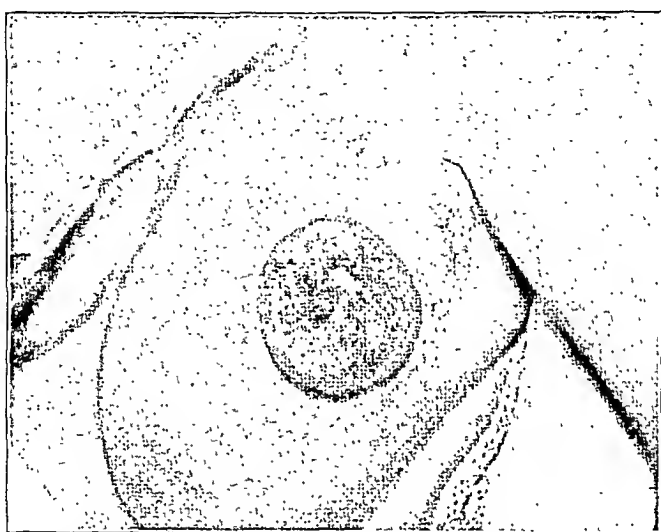


Fig. 3.—Fungating comedo carcinoma of the breast of over two years' duration in a woman 55 years of age. (From Bloodgood, J. C.: *Am. J. Cancer* 22:842 [Dec.] 1934.)

sometimes noted. The tumor remains movable. Even when the growth is larger than a large grapefruit and involves almost the entire breast, there will be no fixation to the wall of the chest. Several tumors may be found in the same breast. In three instances similar tumors were found in both breasts.

#### RESULTS OF TREATMENT

Of all the forms of carcinoma of the breast, comedo carcinoma offers the most favorable prognosis. At the time the data for this report were secured there were 85 per cent of five year cures in the group of cases observed by us. The majority of the patients living more than five years after operation have remained well for ten years

TABLE 1.—Data on Forty-Seven Cases of Comedo Carcinoma

Case No.	Age, Yr.	Duration of Growth	Clinical Findings	Operation	Result
1	53	4 mo.	Pain in lateral portion of breast; discharge from nipple; tumor 6 cm. in diameter	7/22/37: Excision 8/11/37: C.C.*	Well in 1937
2	44	7 yr.	Hard and freely movable tumor 6 cm. in diameter	3/19/34: Excision	Well in Sept. 1937
3	35	3 mo.	Tumor of left breast near nipple; two similar lumps; comedos in gross specimen; discharge from nipple; tumor 0.5 cm. in diameter	July 1936: Biopsy; excision Oct. 1936: C.C. for recurrence	Well in Sept. 1937
4 (Case 1 of text)	63	7 yr.	Fungating tumor the size of a grapefruit	2/23/34: O.C.	Died 3/10/34 postoperatively
5	46	1 yr.	Tumor 1.5 cm. in diameter near a cyst	1935: C.C.	Well in July 1937
6 (Case 5 of text)	44	5 yr.	Tumor 2 cm. in diameter near nipple	6/27/33: C.C. 4/../34: C.C. of other breast	Well in Sept. 1937
7	29	3 mo.	Tumor 1 cm. in diameter near nipple	10/15/34: Excision 9/21/36: C.C. for recurrence	Well in Sept. 1937
8 (Case 3 of text)	53	1 mo.	Tumor 3 cm. in diameter	11/14/32: C.C.	Well 12/5/35; lost from observation in 1937
9	37	1½ mo.	Tumor 6 cm. in diameter near nipple; no discharge	5/13/32: C.C.	
10	38	9 mo.	Tumor 9 cm. in diameter near nipple; discharge	1/8/31: Excision 1936: C.C. for recurrence	Well in Sept. 1937
11	45	Routine finding	Tumor 2 cm. in diameter; comedos in gross specimen	5/21/27: C.C.	Well in Sept. 1937
12	52	2½ mo.	Tumor 2 cm. in diameter near nipple	12/ 5/28: C.C.	Died from other causes 8 yr. after operation
13 (Case 4 of text)	48	3½ yr.	Tumor involving one half of breast; sanguineous discharge from nipple	5/31/27: C.C.	Died in 1932, 5 yr. after operation, of metastases
14	53	1 yr.	Tumor 3 cm. in diameter; freely movable; atrophy of fat	6/17/26: Excision	Well in Sept. 1937
15	56	2 mo.	Tumor 2.5 cm. in diameter near nipple; discharge	9/16/24: C.C.	Well in 1930
16	67	1 mo.	Tumor near nipple	6/ 6/24: C.C.	Died in 1930, 6 yr. after operation, from other causes
17	40	2 wk.	Tumor 2 cm. in diameter in right breast, just behind and above nipple	Dec. 1923: Excision Dec. 1924: C.C. for recurrence	Well in 1937, 14 yr. after first operation
18	39	3 mo.	Tumor 3 cm. in diameter near nipple; affected breast largest in midzone, with overlying red skin; no discharge; growth circumscribed but not encapsulated near skin; atrophy of fat	10/13/23: C.C.	Well in 1937, 14 yr. after operation
19	45	3 yr.	Tumor 8 cm. in diameter, and 3 cm. from nipple; patient kept under observation for 1 yr.	12/ 5/22: C.C.	Died 4/26/37 from other causes
20	42	1 day	Tumor 2 cm. in diameter	7/13/22: C.C.	Well 4/13/37, 15 yr. after operation
21	45	10 mo.	Tumor 6 cm. in diameter; discharge from nipple	5/21/20: C.C.	Well in 1930, 10 yr. after operation
22	49	2 yr.	Tumor beneath nipple; nipple retracted; dimpling and itching; mass in axilla for 3 mo.	4/ 6/20: C.C.	Lost from observation
23	39	1½ yr.	Tumor the size of a grapefruit; discharge from nipple	1918: Excision 1919: C.C. for recurrence	
24 (Case 2 in text)	34	1 yr.	Tumor 4 cm. in diameter	3/22/17: C.C.	Well in 1937, 20 yr. after operation

\* In this table and in tables 2 and 3, C.C. indicates complete operation for carcinoma.



Bloodgood,<sup>2</sup> in a note to the article published in the *American Journal of Cancer*, stated:

No new cases are added and all the evidence is that the pure comedo-adenoma does not give rise to metastases, and can be cured by excision of the local tumor only. When the tumor is of fungous nature or is too large for local excision, irradiation should be tried first.

The figures which we have presented would seem to show that eventually local operation has been followed by recurrence, but they also indicate that when a radical operation is performed a year or more after local excision because of recurrence a cure has resulted in spite of axillary metastases. Because of the difficulties encountered in determining the malignant potentialities of the duct tumor designated as comedo-adenoma, it would seem best to do a primary radical operation in all tumors of this type.

#### HISTOLOGIC DESCRIPTION

Comedo carcinoma arises from small oval cells with dense nuclei and scanty cytoplasm. These resemble the basal cells of the epidermis. There are numerous intermediate cell forms with increasing amounts of cytoplasm showing a differentiation into duct epithelium with an irregular secretory border. These cells form a thick lining or wall in the ducts. The larger secretory epithelium surrounds the central lumen of the duct, which contains secretory débris; the smaller basal cells rest on a basement membrane, which sharply demarcates the duct epithelium from the periductal fibrous tissue (fig. 4). The nuclei of the tumor cells are small and dense and in general show no conspicuously malignant features. All of the duct channels throughout one or more quadrants of the breast may show this characteristic hyperplasia of the lining epithelium. The tumor cells not only line preexisting ducts but form new secretory channels, so that small secondary openings appear in the cross-sections of the lining epithelium of the larger ducts. The tumor grows slowly and metastasizes late, if at all, to axillary lymph nodes. In cases in which metastases occur the epithelium in the lymph nodes shows the characteristic thick-walled ducts lined by secretory epithelium with numerous transitions toward basal cells. This characteristic histologic appearance of the metastases (fig. 6) indicates clearly that the tumor cells are capable of forming new ducts and are not simply invading preexisting ducts.

In the typical comedo carcinoma the tumor cells are confined by a basement membrane and form epithelial channels with solid or thick walls; invasion of fat or fibrous tissue is inconspicuous or absent. The

TABLE 3.—*Data on Thirty-Nine Cases of Combined Comedo and Scirrhus Carcinoma*

Case No.	Age, Yr.	Duration of Growth	Clinical Findings	Operation	Result
1	55	1 yr.	Tumor 2 cm. in diameter in inner quadrant of breast; freely movable; no discharge	1/30/36: Exeision 2/26/36: C.C.	Well in Sept. 1937
2	42	5 yr.	Tumor 5 by 4 by 2 cm. below nipple of left breast; attached to skin; no discharge; dilatation of veins	12/14/32: C.C.	Well 9/17/37
3	23	3 mo.?	Tumor 6 cm. in diameter; rapid growth	6/ 5/34: Exeision	Well to 1936
4	54	2 mo.	Tumor 2 cm. in diameter medial to nipple; no discharge	5/ 1/34: Amputation only; preoperative irradiation, 1,800 roentgens	Died in Sept. 1937 of metastases to bone and skin
5	40	1 wk.	Tumor 2 by 3 cm. in upper inner quadrant of right breast; no discharge	4/30/32: C.C.	Well 10/1/37
6	65	6 wk.	Tumor 2.5 cm. in diameter in upper quadrant of right breast; dimpling; no discharge	1/29/32: C.C.	Well 9/17/37
7	63	6 wk.	Tumor 8 cm. in diameter in outer upper quadrant of left breast; hard, nodular and attached to skin	11/20/30: C.C.	
8	52	7 wk.	Lump in left breast; hard and firm	10/ 4/32: C.C.	Died in May 1933 of metastases to liver
9	25	3 wk.	Tumor; pain	6/10/30: C.C.	
10	54	3 wk.	Tumor; pain	3/ 3/30: Biopsy 3/29/30: C.C.	Well in Aug. 1936
12*	55	1 yr.	Tumor 6 cm. in diameter; intermittent swelling	3/16/26: C.C.	Died in June 1929 of metastases to lungs
13	47	6 wk.	Lump in nipple zone the size of a silver dollar; lump in axilla	10/15/26: C.C.	Died 3/4/29
14	45	6 mo.	Tumor 2 cm. in diameter in right breast; tumor 1.5 cm. in diameter in right breast	8/ 1/25: C.C.	Died in 1930
15	50	5 mo.	Tumor involving entire breast; redness and pigskin appearance of skin; retraction of nipple; irritation	2/17/25: C.C.	Died in 1926 of carcinosis
16	41	3½ mo.	Lump in breast with retraction of nipple; lump in axillary gland for 1 wk.	11/29/24: C.C.	Died in June 1925
17	52	4 yr. 2½ yr.	Nipple retracted; crust and mass beneath nipple	10/20/24: C.C.	Died in Feb. 1929 of pulmonary metastases
18	65	3 yr.	Tumor involving entire left breast; mass beneath nipple	10/10/23: C.C.	Died in 1925 of metastases to liver
19	32	6 mo.	Tumor 1.5 cm. in diameter in left breast	9/29/23: C.C.	Died in 1925 of metastases to lung
20	38	3 yr. (axilla) 3 wk. (breast)	.....	.....	Died in 1932 of metastases
21	51	.....	Tumor 7 cm. in diameter beneath nipple; comedos in gross specimen	2/27/23: C.C.	
22	32	3 wk.	Tumor 4 cm. in diameter in left breast	1/—/23: C.C.	Died in 1923 of metastases to lungs
23	41	12 yr. (pain) 6 mo. (tumor)	Tumor 2.5 cm. in diameter in upper outer quadrant of breast; atrophied over tumor	12/27/22: C.C.; postoperative irradiation	Died 4/29/36 of metastases to bone

In duct carcinoma showing a histologic relation to Paget's cancer, the tumor cells approach squamous epithelium in type. The tumor cells have abundant cytoplasm and large dense or vesicular nuclei with numerous mitoses. Multinucleated giant tumor cells are common. Areas of central necrosis are seen within duct channels lined by such highly malignant epithelium (fig. 7). The tumor invades the large ducts, and ulceration of the nipple may occur, giving the classic clinical picture of Paget's carcinoma. The growth of the tumor is rapid, and

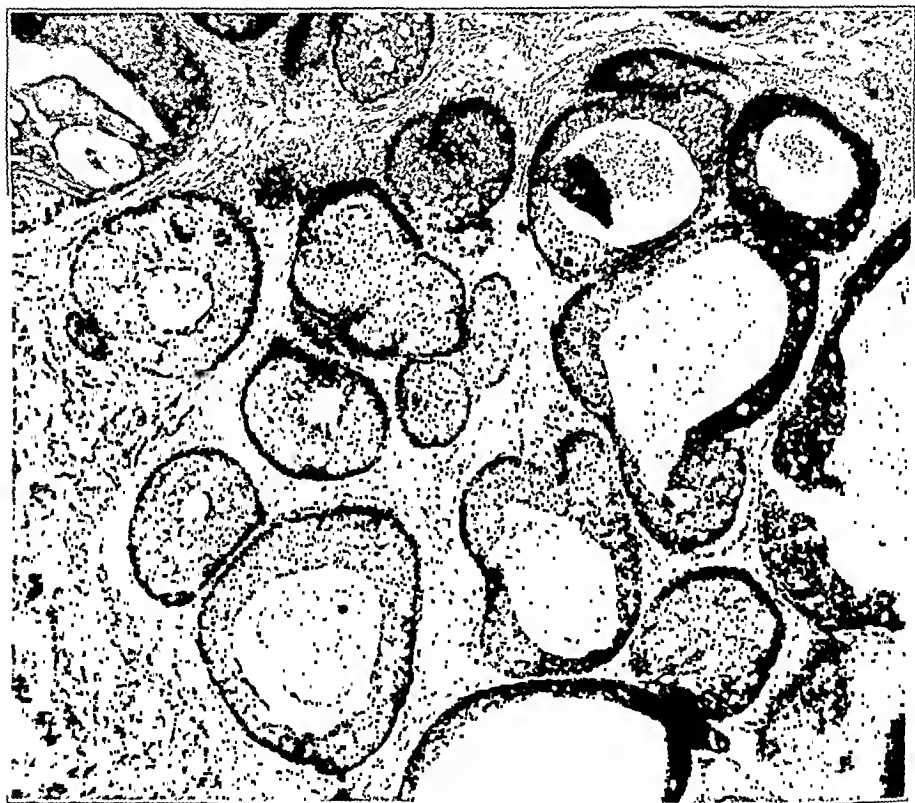


Fig. 4.—Photomicrograph of a typical comedo carcinoma showing ducts filled with epithelial plugs. Small new ducts are being formed in the epithelial plugs.

the prognosis is poor. This type of duct cancer is more closely allied in its behavior to Paget's cancer of the nipple than to comedo carcinoma.

In typical scirrhus carcinoma (infiltrating adenocarcinoma) areas of invasion resembling comedo carcinoma may be found occasionally in the smaller ducts. This tumor should not be confused microscopically with true comedo cancer. In carcinoma arising in the smaller ducts and terminal tubules there will be found under the microscope areas resembling comedo carcinoma. But invasion of fat and fibrous tissue by

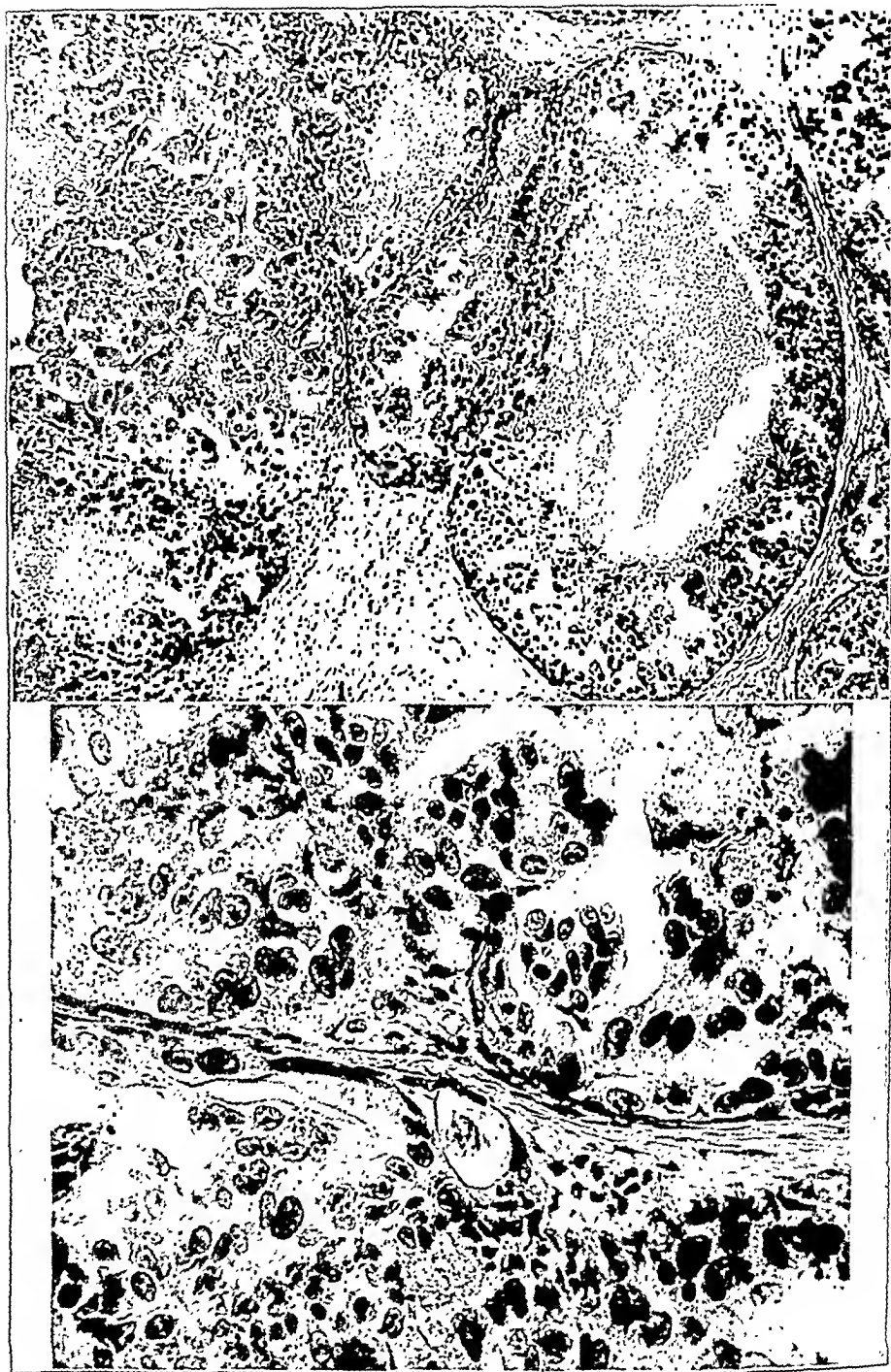


Fig. 7.—Medium and high power photomicrographs of a duct carcinoma, showing large malignant cells similar to those seen in Paget's disease of the nipple. This type differs from the comedo carcinoma in clinical course and in prognosis.

islands of scirrhous carcinoma is a prominent feature (figs. 8 and 9) which allows this growth to be differentiated microscopically from comedo cancer.

Many of the cases in the literature described as instances of duct cancer are examples of slowly growing adenocarcinoma developing in intraductal papilloma. Although arising within the confines of the ducts, the epithelium giving rise to such a tumor has acini-forming potentialities and gives rise to adenocarcinoma rather than to comedo carcinoma.

to cases of so-called silent tumor, but prefer it as a preliminary measure in certain cases in which neurologic examination provides data of localizing value. From a surgical standpoint it is often not enough to localize a tumor roughly by means of the neurologic information. Not only may the neurologic information be grossly misleading, but it may encourage the surgeon to explore somewhat eccentrically the bulk of a tumor. He then finds it necessary to widen an already extensive craniotomy incision for adequate exposure. The close similarity in the neurologic findings between a tumor of a cerebellar hemisphere and one in the contralateral frontal lobe is commonly known. A large meningeal fibroblastoma may cause symptoms and signs which are inadequate for the preparation of the optimum exposure. The two following cases are illustrative of this situation:<sup>3</sup>

#### REPORT OF CASES

CASE 1.—E. S., a white woman aged 46, complained of diminished visual acuity and headache, which had been present for six months. She had spells of jerking of the right hand and arm during which she would appear dazed but would nod when spoken to. She was beginning to have strange ideas. Bilateral papilledema and bitemporal hemianopia were present. At times there appeared to be a loss of cortical sensation on the right. A roentgenogram of the skull revealed questionable changes in the midsagittal, posterofrontal region. A ventriculogram verified these changes, for it showed a bilateral filling defect of the anterior horns and part of the body of both ventricles (fig. 1*A*). On the diagnosis of a meningioma about the sagittal sinus a suitable osteoplastic flap was prepared, and a meningioma bilateral to and invading the sinus, weighing 120 Gm., was removed (fig. 1*B*). It was necessary to remove a segment of the sagittal sinus  $2\frac{1}{2}$  inches (6.3 cm.) long. The patient fully recovered and is oriented and able to do her own housework.

CASE 2.—M. S., a white woman aged 48, had had weakness of the left arm and leg for nine months and blurred vision for one month before examination. During the last month she had had convulsions of the left arm and leg, which spread to the left side of her face.

Examination revealed bilateral papilledema with diminished visual acuity and a slight bitemporal cut in the visual fields. There were hemiparesis and diminished cortical sensation on the left side. A roentgenogram revealed a questionable erosion at the vertex of the skull. A ventriculogram showed a filling defect of

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3. Dr. Clarence Van Epps, Professor of Neurology, cooperated in this study by referring a large group of patients to me. Many of the routine procedures presented were performed by members of the departments of ophthalmology, otolaryngology, roentgenology and pathology.

A tumor situated largely in one of the so-called silent regions may cause neurologic signs as a result of pressure on nearby structures or as a result of edema remote from the tumor. In such an instance the optimum exposure will not necessarily be one centered over the anatomic counterpart of the signs. While it is true that edema remote from a tumor will distort the ventricles, localization of the tumor will ordinarily not be difficult.

Occasionally, accepted signs will falsely indicate the side on which the pathologic condition is situated.

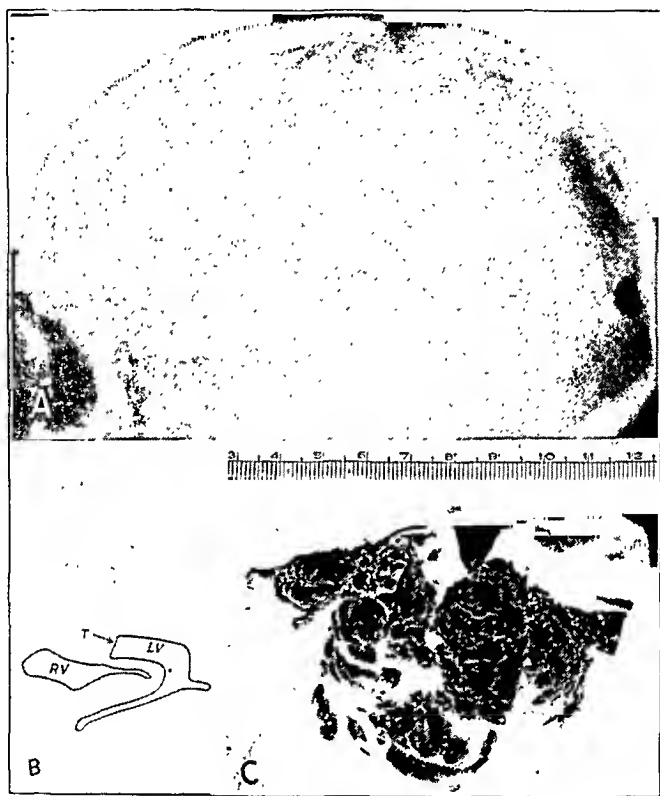


Fig. 2 (case 2).—*A* shows a ventriculogram demonstrating depression of the right ventricle and obliteration of the anterior aspect of the left ventricle. The skull is eroded in the region of the vertex. *B* is a diagrammatic representation of *A*. The right ventricle is indicated by *RV*, and the left ventricle by *LV*. *T* indicates the margin of filling defect due to the tumor. *C* shows a meningeal fibroblastoma. Note the cross-section of sagittal sinus which is infiltrated with the tumor in the upper left. The scale is in centimeters.

CASE 3.—J. K., who was thought to have a chronic subdural hematoma, presented increased intracranial tension, a stiff but weakened right arm and a dilated left pupil. These signs indicated a lesion on the left side. A preliminary ventriculogram prevented a serious surgical error, for the hematoma was in the right frontal region.

with a benign tumor. If this were true, it would be of value, in that when the whole hemicerebrum, ventriculographically speaking, seemed to be involved, the evidence would be in favor of an infiltrating tumor. The extensive shift of the ventricular system would thus be due in a large measure to swelling of the white matter. With the feeling that



Fig. 3 (case 5).—*A* shows the anteroposterior view of a ventriculogram, demonstrating a marked shift of the system to the right and obliteration of the left anterior horn. *B* is a diagrammatic representation of *A*. The horizontal cross-hatch is the right anterior horn, the vertical cross-hatch represents parts 2 of the ventricles,<sup>2a</sup> and the stipple is part 3 of the right ventricle. The right temporal horn is indicated by *TH*, the midsagittal plane by *MS* and the perforator openings by *Per*. *C* is the section of the brain which is anterior to the ventricles showing the meningeal fibroblastoma. The tumor is not shown in its greatest diameter. Attachment to the falx was more anteriorly placed. There is extensive edema of the white matter of the left hemisphere, which existed in the entire anteroposterior diameter of the left hemisphere.



is well to inject some air after the fluid has ceased to flow. Roentgenograms will then give precise information concerning the location of the cyst.



Fig. 4 (case 6).—A meningeal fibroblastoma is shown on the left. From the appearance of the ventricles it is logical to suppose that a ventriculogram would have indicated a more accurate and direct exposure than did the neurologic findings.

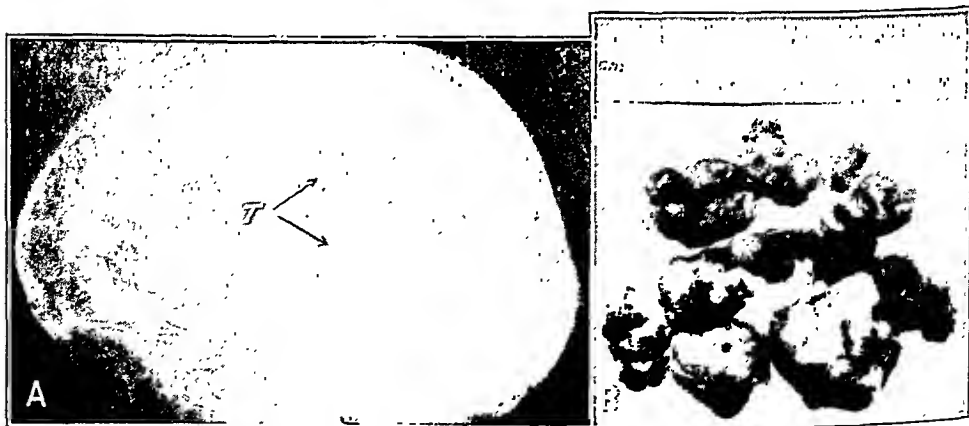


Fig. 5 (case 7).—*A* shows a symmetrical hydrocephalus except for the filling defect, *T*, in the anterior aspect of the left lateral ventricle. *B* shows portions of the mural tumor (astrocytoma) that were removed.

CASE 8.—V. O., a white woman aged 19, presented symptoms of tumor consisting of headaches, vomiting, dizziness, bilateral choked disks and spinal fluid pressure of 20 mm. of mercury in the prone position. There were no signs of

of air and obtained satisfactory visualization. When the intracranial pressure has been reduced to atmospheric pressure or, as in these three cases, if an open ventricular needle is left in the ventricular system, such a procedure is not felt to be particularly hazardous. Two cases, those of L. S. and A. McD. (cases 14 and 23), in which a supplementary spinal injection was done are outlined in the case reports, and the other case was one of essential hypertension with marked increased intracranial tension. A ventriculogram revealed normal lateral ventricles, which in such an instance might justly be taken as sufficient information, but a normal third ventricle, aqueduct of sylvius and fourth ventricle were clearly demonstrated by a supplementary spinal injection.

Normal ventriculograms do not contraindicate the presence of a tumor. Patients whose ventriculograms are normal will, however, usually come to the physician because of symptoms and signs other than those attributable to the usual tumor. The histories of these patients and the results of neurologic examination overrule a normal ventriculogram, and many such cases constitute the instances of early tumor of which the neurosurgeon dreams. I have observed three such cases within the past eighteen months. One, that of J. H., is discussed in the case reports (case 11).

Following are descriptions of two cases of tumor in which there were normal ventriculograms.

CASE 9.—W. C., a 23 year old white man, presented a history of petit mal seizures of increasing frequency and severity which had been present for nine years. The history and the seizure pattern indicated the anatomic substratum to be that of the right frontal lobe, particularly the right frontal adverse field. The ventriculogram and the intracranial pressure were normal, but a diagnosis of a nondeforming astrocytoma of the right frontal lobe was made. This was verified at operation, and a resection of the lobe was rewarded with complete cessation of seizures. (There has been no recurrence at the time of this report, eighteen months later.)

CASE 10.—L. I., a woman aged 40, presented a short history of migraine-like headache and brief seizures consisting of flashes of colored light in the left visual field, associated with transient ataxia of the left arm and leg. There was a small homonymous cut in the left visual field. The intracranial pressure and the ventriculogram were normal. Exploration was carried out, and  $1\frac{1}{2}$  inches (3.8 cm.) of the right occipital lobe was resected. When the tissue was sectioned, an angioma about 1 cm. in diameter was disclosed. The angioma was situated in the midregion of the area striata and showed evidence of old repeated hemorrhages in its vicinity (fig. 7).

#### FACTORS CONCERNED IN THE TECHNIC AND MANAGEMENT OF VENTRICULOGRAPHY

1. I prefer to make an incision with a perforator over each posterior horn with the patient in the cerebellar position. Incisions  $\frac{3}{4}$  (1.8 cm.) to 1 (2.5 cm.) inch long are made in a sagittal plane about 1 inch

three hundred intracranial operations. The source of one of the infections was a leak of the cerebrospinal fluid, while that of the other infection was an incisional hematoma improperly managed.

Anesthesia other than a local injection of a 2 per cent solution of procaine hydrochloride is seldom needed, even for small children. The incisions are spread by means of a three prong self-retaining mastoid retractor. A shallow beveled perforator is used, and the inner opening of the trephine is rounded off with a suitable blunt instrument so as to expose an area of dura about  $\frac{1}{8}$  inch (0.3 cm.) in diameter. Only the dura is incised with a pointed scalpel, and the incision is spread with the blunt point of a ventricular needle. A single silk suture in the galea and several deep sutures in the skin suffice for the closure. The patient is transferred to a cart and is controlled by an assistant; the patient is placed on his side with his head lying on a sand bag. The suspected normal side is placed dependently. After a loose draping of sterile towels, the dependent ventricle is entered. By means of a rubber tube connector, a three way stopcock and an easy-working 20 cc. syringe, the injection of air is made.

2. In consideration of the contrast medium used for visualization of cerebral topography, gas is at present far superior to any other known medium. I prefer to use atmospheric air, since no serious objection to its use relative to other gases has ever been presented and the working equipment is reduced to a simple outlay.

A complex apparatus for spinal injection of air has recently been devised that is deserving of consideration.<sup>6</sup> The apparatus is designed to replace the cerebrospinal fluid with gas by a continuous flow. The machine is mechanically ingenious and novel in performance. Disadvantages in the operative procedure are unnecessary additional apparatus, the necessity of two lumbar punctures and the fact that performance depends on free unhampered flow of cerebrospinal fluid, which often does not obtain. The high quality of the pneumogram, which is attributed to the apparatus, is undoubtedly due to the mechanical courage of the apparatus in making a complete injection rather than to any inherent property of the machine.

3. The question often arises as to how much air is injected into the ventricles. This obviously depends on the capacity of the ventricles. An attempt is made to replace all of the available fluid with air in the case of either ventricular or spinal injection. Fluid is replaced by air in quantities of 5 to 10 cc. One should avoid creating a negative pressure by suction or an excessively increased pressure by force, but I do not believe it important that an increased intracranial pressure be maintained.

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6. von Storch, T. J. C.: On Technique of Encephalography with Special Reference to Use of Apparatus, *Am. J. Roentgenol.* **35**:78-92, 1936.

position. Unless enough fluid is replaced by air so that when the patient is in the lateral position there is more than enough air to fill the upper ventricle, obviously the third ventricle will not be visualized.

4. The ideal situation is one in which the operation is performed as soon as the roentgenograms are developed and interpreted. This should ordinarily not require more than twenty minutes from the time the roentgenograms are made. It is needless to say that the surgeon should be skilled in interpreting the ventriculograms. It is imperative in neurosurgery, more than in any other field of surgery, that all data and information concerning the problems be encompassed in a single mind in order to attain that which is difficult but possible.

I have yet to be confronted with an untoward reaction if the ventricles have proved to be normal, but with the presence of a tumor that has not been operated on the postventriculographic period may be disturbing. Postponement of the operation until the following day is a gamble against heavy odds. Ventriculography in the event that a tumor is found should be regarded as a part of the major operation, which should be carried to some conclusion at the earliest possible moment. The fact per se that air is injected into the ventricles is of little consequence, but the inevitable disturbance of relationships of tension that have been so precariously balanced between the tumor and its environment is of extreme importance.

If for some reason the craniotomy is postponed, the patient should be given special nursing care and frequent records should be taken of the pulse, respiration and blood pressure. A fluctuating blood pressure is an ominous sign of endangered vital centers.

If the ventricles are not greatly dilated and all channels are open for free circulation of cerebrospinal fluid, the air will be absorbed satisfactorily without intervention. It is my opinion that the absorption is accomplished by solution of the gas in the cerebrospinal fluid. The gas is then carried into the blood stream in a state of solution. If the ventricles are greatly dilated, increasing tension may manifest itself beginning one or two hours after the injection. In this case air should be allowed to escape through a ventricular needle by repeated punctures if necessary.

If there is some obstruction in the circulation of cerebrospinal fluid, air may remain in the ventricles indefinitely and be the cause of a febrile reaction and increased tension. In such a case it is imperative that the air be removed by the surgeon.

There will always be a percentage of cases of tumor of the brain of such a nature that death will be inevitable whether the patient is operated on or not. This outcome cannot always be predicted, however, except in retrospect. Death in such instances may occur for no other reason than the fact that a high tension has suddenly been released to

rect diagnosis was made on the clinical and roentgenologic findings in all but three cases. Endocrinologic and neurologic signs may vary considerably. Primary atrophy of the optic nerve and bitemporal defects of the visual fields are extremely valuable indications of suprasellar tumor in adults. For patients in adolescence or preadolescence, however, it is often impossible to obtain visual fields, and the marked papilledema often associated with a suprasellar cyst may nullify the importance of moderate defects in the fields. In Beckman and Kubie's cases, papilledema and hydrocephalus occurred only in adolescence.

Another feature pointing strongly to the diagnosis of suprasellar cyst is the changes seen in and above the sella in the roentgenogram. McKenzie and Sosman<sup>9</sup> and Cushing<sup>10</sup> pointed out that suprasellar or intrasellar opacities are seen in 70 to 80 per cent of the cases.

There is a certain percentage of cases, however, in which the diagnosis will be indefinite. This is true of two of the cases which are to be reported, those of J. H. and G. T. (cases 11 and 13). It is possible but rare that a diagnosis of a suprasellar tumor will be falsely indicated, as in the case of A. R. discussed earlier in the paper (case 4).

Bailey<sup>11</sup> has pointed out that a suprasellar tumor can produce cerebellar symptoms. Hence in cases in which a diagnosis is not definite or possible, an adequate ventriculogram is in order, which will reveal the tumor.

A discussion of tumors of the thalamus is included in this paper because they produce filling defects in the third ventricle. A thalamic syndrome has been described,<sup>12</sup> but ventriculographic evidence is most welcome. In the case of J. P. (case 15), exploration was indicated. It is conceivable that the tumor may be a benign tumor of the third ventricle pressing on the thalamus, although I have been unable to find a report of such a growth which was accompanied with Roussy's thalamic syndrome. An extremely interesting case in which there were autonomic seizures has been reported by Penfield.<sup>13</sup>

It may be said that tumors of the pineal body, corpora quadrigemina and third ventricle present symptoms that not only are largely due to hydrocephalus but are often so closely allied that differentiation of the

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9. McKenzie, K. G., and Sosman, M. C.: The Roentgenological Diagnosis of Cranio-Pharyngeal Pouch Tumours, *Am. J. Roentgenol.* **11**:171-176, 1924.

10. Cushing, H.: The Intracranial Tumours of Preadolescence, *Am. J. Dis. Child.* **33**:551-584 (April) 1927.

11. Bailey, P.: Concerning the Cerebellar Symptoms Produced by Suprasellar Tumours, *Arch. Neurol. & Psychiat.* **11**:137-150 (Feb.) 1924.

12. Roussy, G.: La couche optique (étude anatomique, physiologique et clinique), Thèse de Paris, no. 165, 1907.

13. Penfield, Wilder: Diencephalic Autonomic Epilepsy, *Arch. Neurol. & Psychiat.* **22**:358-374 (Aug.) 1929.

extrication of the tumor is a conquest of unmatched reward. It is here that technical ideals in neurosurgery reach a high point, for one is dealing with a lesion that is dangerous not by reason of its pathologic nature, but by reason of its position, which makes it incompatible with life. That the cyst or tumor can be successfully removed in a high percentage of cases is now an established fact, and thus is added another brilliant chapter to neurosurgery.<sup>16</sup> The diagnosis will always constitute a brilliant achievement in each individual case. I feel that a successful diagnosis can be made consistently by using ventriculography to its fullest advantage.

A masterly treatise on benign tumors in the third ventricle has been prepared by Dandy.<sup>17</sup> It deals with the situation from the diagnostic, operative and pathologic standpoints. The importance of the complete use of ventriculograms is emphasized. In four cases of the twenty-one which he reported, Dandy passed up a nonvisualized third ventricle to perform a cerebellar exploration, but he found it was necessary to retrace his steps and finally uncover the tumor through a third ventricle approach.

Formerly, symmetrically dilated communicating lateral ventricles were considered sufficient indication for a cerebellar exploration, and errors of making such explorations were considered excusable. To explore the cerebellum now without having made every effort to visualize the third ventricle is to neglect adequate diagnostic methods.

From a pathologic standpoint benign tumors of the third ventricle are classified as follows: colloid cysts, which comprised five of the twenty-one of the tumors in Dandy's series and which probably arise from the ependymal epithelium; a heterogenous group of tumors, comprising circumscribed ependymal gliomas, pearly tumors as reported by Penfield,<sup>13</sup> simple cysts and papillomas of the choroid plexus, and an unclassified group of circumscribed grossly benign tumors which it is thought arise from undifferentiated cell rests.

Tumors of the pons are inoperable, and I have never made a ventriculogram in a case of such a growth. The diagnosis may be suspected owing to early and advanced clinical signs, but in case of doubt it is logical to suppose that the aqueduct of Sylvius would be shifted backward and its normal curvature emphasized.

Ventriculography has relatively little importance in the diagnosis of tumors of the eighth nerve, since the clinical syndrome is definite.

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16. McLean, A. J.: Paraphysial Cysts, *Arch. Neurol. & Psychiat.* **36**:485-513 (Sept.) 1936. Masson, C. B.: Complete Removal of Two Tumors of the Third Ventricle with Recovery, *Arch. Surg.* **28**:527-537 (March) 1934.

17. Dandy, Walter E.: *Benign Tumors in the Third Ventricle of the Brain: Diagnosis and Treatment*, Springfield, Ill., Charles C. Thomas, Publisher, 1933.

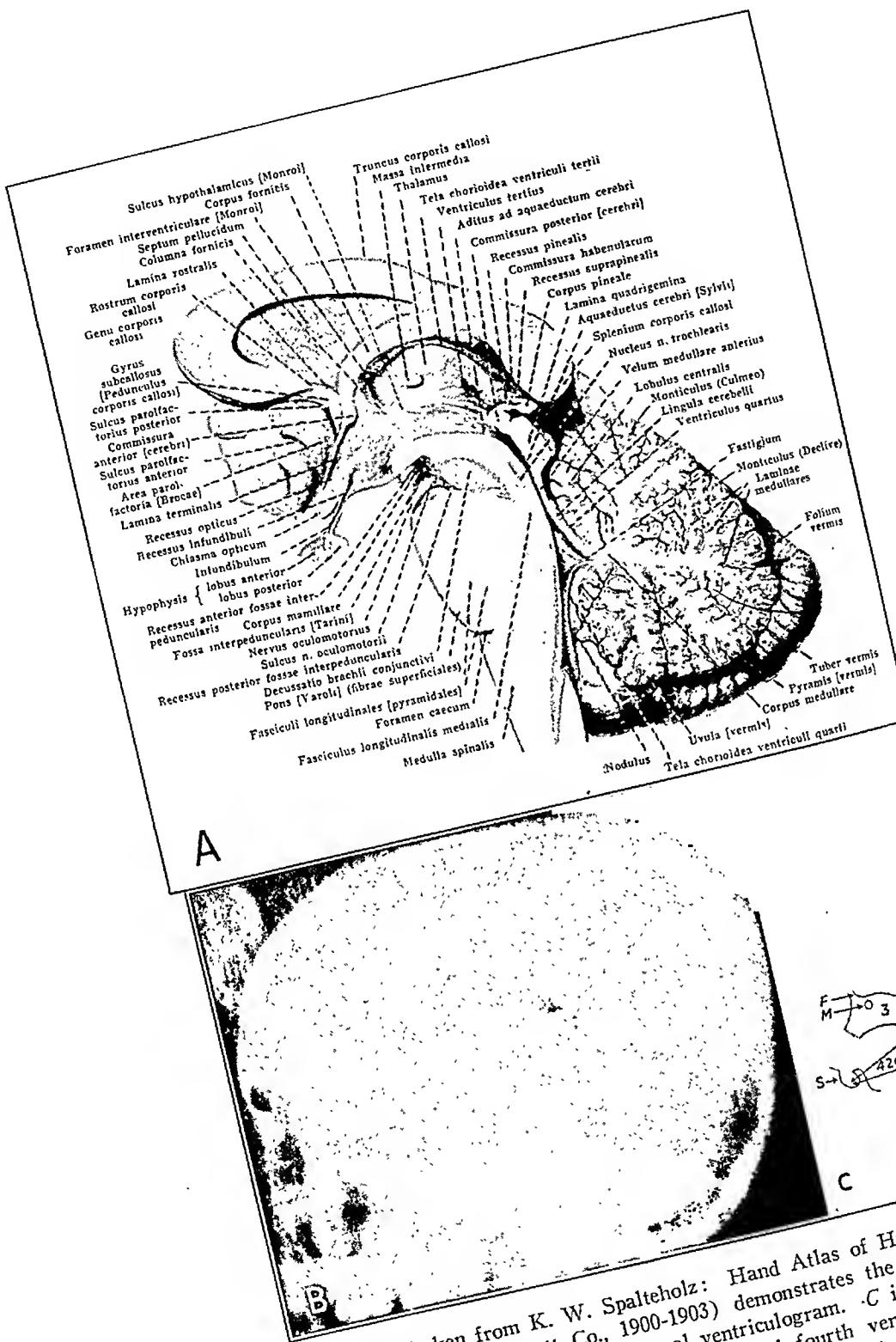


Fig. 8.—A (taken from K. W. Spalteholz: Hand Atlas of Human Anatomy, Philadelphia, J. B. Lippincott Co., 1900-1903) demonstrates the relations of the normal third ventricle. B shows a normal ventriculogram. C is a diagrammatic representation of the third ventricle, aqueduct and fourth ventricle seen in B. F indicates foramen of Monroi; M, massa intermedia; 3, third ventricle; SPR, suprapineal recess; PR, pineal recess; A, aqueduct of Sylvius; 4, fourth ventricle; N, invagination of the fourth ventricle due to the cerebellar nodulus; S, sella turcica.

## REPORT OF CASES

TUMOR IN OR ABOUT THE THIRD VENTRICLE<sup>20</sup>

CASE 11 (*Suprasellar Cyst*).—J. H., a man aged 34, was referred to the department of ophthalmology in August 1935 by Dr. Mark C. Jones, of Boone, Iowa. The patient complained of diminishing visual acuity and headache, which had been present for several months. Bright lights hurt his eyes, and there were burning and smarting when he attempted to read. Headaches were of daily occurrence, lasted from one to three hours and were augmented by jarring or stooping. The headaches were usually in the right temporofrontal region. There was no nausea or vomitng. Examination revealed a visual acuity of 6/21 in the left eye and 6/21 in the right. The visual fields showed a bitemporal hemianopia. The patient was transferred to the department of neurology, where an encephalogram was made (fig. 10). There was good filling of the ventricles and subarachnoid spaces in the anteroposterior view, and they were regarded as normal. (The third ventricle did not show in the lateral view.) The patient was transferred to the neurosurgical service, however, since it was thought that the findings in the visual fields were more significant than the negative encephalogram.<sup>21</sup> The chiasm and the suprasellar region were explored by the right subfrontal route.<sup>22</sup> Preparatory to elevation of the frontal lobe, a ventricular needle was passed toward the anterior horn. When the stylet was withdrawn, 10 cc. of opalescent yellow fluid came forth, and without the needle's being moved this fluid was followed by clear cerebrospinal fluid. The yellow fluid subsequently proved to contain 310 mg. of cholesterol per hundred cubic centimeters. The suprasellar region revealed nothing abnormal, and with the evidence at hand I did not feel justified in sectioning the right optic nerve for a more thorough exploration. The subsequently proved content of cholesterol in the yellow fluid led me to believe strongly, but not conclusively,<sup>23</sup> that I was dealing with a posteriorly placed suprasellar cyst which had probably contracted from view when its contents were evacuated. The patient's headaches were relieved, and his visual acuity was greatly improved. He was discharged temporarily, but he returned in two months with severe headaches and greatly diminished vision. A complete ventriculogram revealed unmistakable evidence of a suprasellar mass (fig. 11), and even though on reexploration the cyst was still not evident, I felt justified in sectioning the right optic nerve. A posteriorly placed cyst with a capacity of about 10 cc. was

20. Only positive findings are discussed in the case histories and examinations.

21. Here the pneumogram cannot be termed strictly "negative," because I did not visualize the third ventricle in the lateral view. Had the third ventricle been visualized, there is no question but that it would have presented the same pathognomonic deformity that was subsequently demonstrated.

The encephalogram is used to denote spinal insufflation of air, while the ventriculogram denotes insufflation of air directly into the ventricles. This universally accepted connotation of the two terms is unfortunate, however, for spinal injection of air may lead to both an encephalogram and a ventriculogram.

22. Heuer, G.: Surgical Experiences with an Intracranial Approach to Chiasmal Lesions, *Arch. Surg.* 1:368-381 (Sept.) 1920; Surgical Approach and the Treatment of Tumors and Other Lesions About the Optic Chiasm, *Surg., Gynec. & Obst.* 53:489-518, 1931. Adson, A. W.: Hypophysial Tumors Through the Intradural Approach, *J. A. M. A.* 71:721-726 (Aug. 31) 1918.

23. I have had five cases of cystic astrocytoma in which the fluid contained a high percentage of cholesterol.



brought into view and entirely removed. The patient recovered uneventfully. It is interesting to note that when a light shone toward the nasal side of his left retina he consistently experienced the sensation of seeing the light with his right (blind) eye.

**CASE 12 (*Suprasellar Cyst*).—**M. J., a white boy aged 5 years, was referred to me by Dr. S. N. Anderson, of Onawa, Iowa, in December 1936. For three months the patient had suffered somnolence, loss of weight, diminution of visual acuity, headaches and staggering gait.

On examination the patient was found to be constantly asleep, but he would arouse somewhat when shaken and give brief answers in a husky voice. He presented a pudgy, somewhat myxedematous appearance, and the skin was noticeably dry. His hands and feet were somewhat spadelike, and his mother informed me that other members of the family had a similar appearance. There were marked bilateral papilledema and paralysis of the right external rectus muscle. The pupils were dilated, of equal size and round and reacted sluggishly to light. The patient refused to walk or to perform most of the usual neurologic tests. The pressure of the cerebrospinal fluid was 250 mm. of water when he was in the prone position. A roentgenogram revealed slight but unmistakable evidence of calcification above the sella, making the diagnosis that of suprasellar cyst. The patient had a slight cough with some nasal discharge, but he was vomiting repeatedly and failing so rapidly that operation without further delay was advisable.

A preliminary ventriculogram was made for the purpose of ascertaining some evidence pertaining to the size of the cyst. If the cyst had proved to be large, aspiration was planned as a preliminary stage. A complete filling of the ventricles was performed, proving free communication between the lateral ventricles but showing complete obliteration of the third ventricle (fig. 12). This indicated the presence of a large cyst, and I had determined to be content at the time with aspiration. A right subfrontal approach was made to the chiasm; a bluish cyst came into view, and 12 cc. of yellow fluid was aspirated. The fluid contained 357 mg. of cholesterol per hundred cubic centimeters. This procedure did not seem to reduce the size of the cyst appreciably, however, and the patient was in such splendid condition under avertin (tribromethanol) anesthesia, which had not necessitated an ether supplement, that the removal of the cyst was begun. It was necessary to section the right optic nerve, after which the usual teasing made it possible to deliver the entire specimen and place a clip on the stalk (fig. 12B). The wound was dry, and the patient was still in a satisfactory condition. His rectal temperature rose to 103 F. in the evening, but it subsequently began to subside. His state of consciousness was encouraging, but his cold became worse. It seemed by the sixth day that there could be no doubt of recovery, but bronchopneumonia developed and the patient died on the seventh postoperative day. Necropsy revealed a dry operative field with no macroscopic damage to the hypothalamus or adjacent structures except for the sectioned optic nerve. There was a perforation in the septum pellucidum about 0.5 cm. in diameter. The cyst had been entirely removed. The lungs revealed bilateral bronchopneumonia.

The tumor proved to be adamantinomatous, and it is of interest that microscopic examination revealed a small amount of infiltration of the tumor into the chiasm. This fact is important in that a suprasellar cyst may be only a part of a tumor of Rathke's pouch and not necessarily a complete entity in itself.

Somnolence was an outstanding feature in this patient's history, as it was in nine of the twenty-one cases reported by Beckman and Kubie.<sup>8</sup>

CASE 14 (*Suprasellar Tumor*).—A. McD., a girl aged 3 years, was referred to the department of pediatrics in July 1935 by Dr. W. L. McConkie, of Carroll, Iowa. The patient complained of diminishing vision, difficulty in walking, an enlarging head, restlessness, nervousness and poor appetite, which had been present for five months.

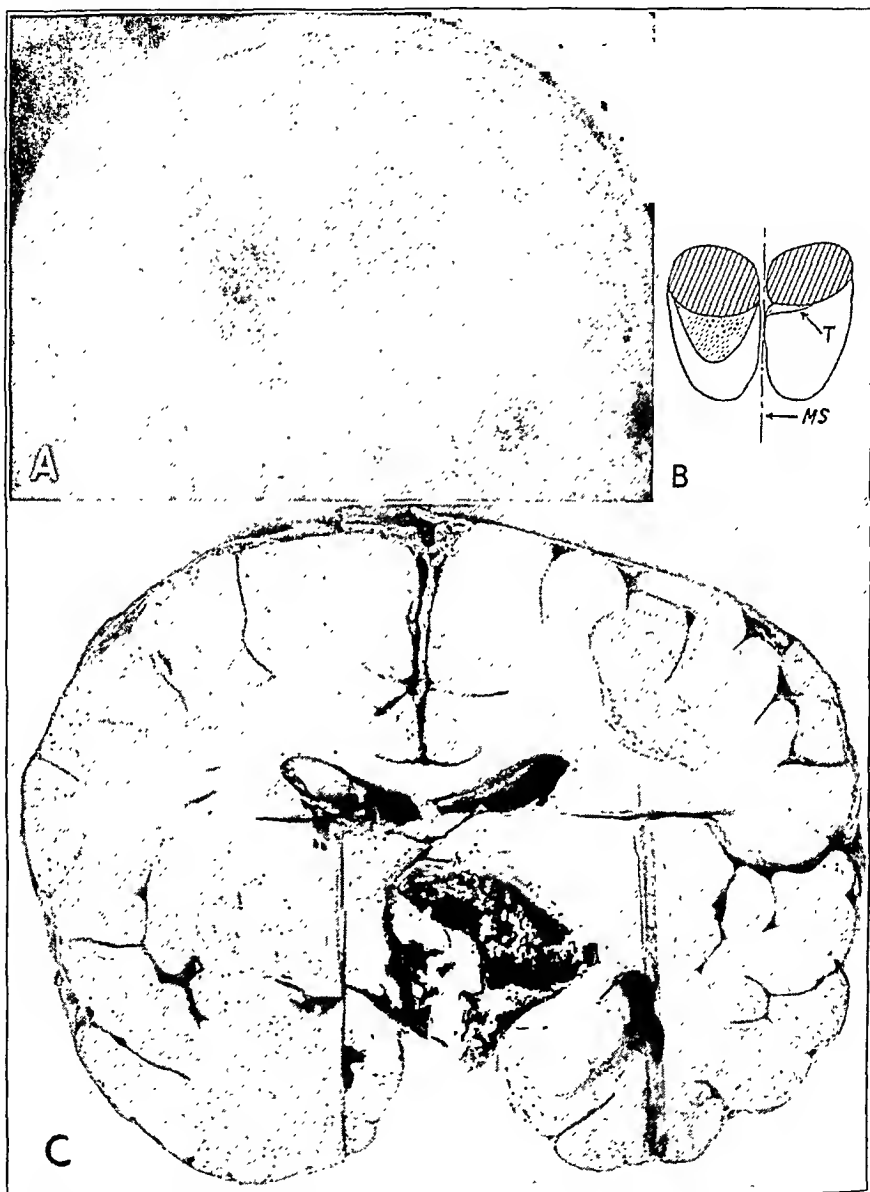


Fig. 13 (case 13).—*A* is a ventriculogram in the anteroposterior view, showing a filling defect in part 2 of the left lateral ventricle and absence of a third ventricle shadow. It was necessary to fill each lateral ventricle independently. Note that the system as a whole is not shifted. *B* is a diagrammatic representation of *A*. *MS* indicates the midsagittal plane, and *T* indicates the margin of the filling defect in part 2 of the left lateral ventricle. *C* is a photograph of the brain demonstrating the large suprasellar cyst.

solid subchiasmal tumor firmly attached to the left optic nerve. Since the frozen section revealed what were taken to be spindle-shaped fibroblasts, it was thought to be a tumor arising from the sheath of the optic nerve and was removed without great difficulty. Hyperthermia and rigidity developed, and the patient died on the second day. Postmortem examination revealed the tumor to be a polar spongioblastoma which arose in the right lenticular nucleus and extended in such a way as to form the growth described (fig. 14 B).

#### TUMOR OF THE THALAMUS

CASE 15.—J. P., a Negro aged 38, was referred to the department of neurology by Dr. E. W. Anderson, of Des Moines, Iowa. The patient complained of staggering gait, dizziness, headache, vomiting and diplopia, which had been present for two months. During the past three weeks he had been irrational and disoriented.

On examination there were general tenderness to percussion of the skull, bilateral paresis of the sixth nerve, advanced bilateral papilledema and dehydration. The patient swayed when his heels were together and his eyes closed. There were continued coreo-athetoid movements of the upper extremities; these were at first interpreted as cerebellar ataxia, but the patient performed the usual cerebellar tests well. There were complete astereognosis on the right side and loss of sensation to light touch. He frequently tried to wipe some phantom object from the right palm. There was overreaction to the light scratch of a pin on the right arm, but this was not present on the left arm. The mental reaction was noteworthy because often when spoken to or engaged in conversation the patient would give rational answers but as soon as he was left to himself he would mutter irrationally and call for his sister and mother.

With this precise clinical account, there was no doubt of the presence of the typical thalamic syndrome such as has been outlined by Roussy.<sup>12</sup> However, there was some doubt concerning localization of the tumor, and a ventriculogram was made (fig. 15 A). There was a sharply defined filling defect in the posterosuperior aspect of the third ventricle, which was felt to be, in order of probability, a tumor of the thalamus, a tumor of the pineal body, or a tumor in the third ventricle. An interhemispherical approach to the third ventricle was made, and when the splenium of the corpus callosum was divided a vascular infiltrating tumor presented. The patient died several hours after the operation, and necropsy revealed a glioblastoma of the left thalamus (fig. 15 B).

#### TUMOR OF THE PINEAL BODY

I have never had a case of pinealoma, but the ventriculogram would be expected to present obliteration of the suprapineal and pineal recesses and to show a filling defect in the posterior aspect of the third ventricle similar to that seen in the ventriculograms of F. L. and J. L., whose cases are now to be presented. Cases of pinealoma have been reported by Dandy,<sup>24</sup> McLean<sup>26</sup> and McConnell and Childe.<sup>18</sup>

24. Dandy, Walter E.: *Operative Experience in Cases of Pineal Tumor*, Arch. Surg. **33**:19-46 (July) 1936; in Lewis, Dean: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, Inc., 1929, vol. 12, pp. 117 and 607.

25. Footnote deleted on proof.

26. McLean, A. J.: *Pineal Teratomas with Report of a Case of Operative Removal*, Surg., Gynec. & Obst. **61**:523-533, 1935.

speech. There was marked secondary atrophy of the optic nerves. The pupils were equal and reacted to light and in accommodation, and the extra-ocular movements were normal, without nystagmus in any direction. There was some stiffness of the neck, and she complained of pain on flexion. There was slight but definite ataxia when the finger to nose test was performed and when she attempted to write. The patient walked unsteadily with a wide base. The reactions to the caloric test, Bárány's test and the audition test were entirely normal. An interesting feature was the fact that the patient always complained of dizziness on turning her head rapidly to one side, though she denied that objects moved or turned before her. While she stood with her heels together and her eyes closed, I turned her head rapidly to one side, and she felt that her feet had rotated in the opposite direction. I flexed her neck, and she felt that her knees had flexed toward her chin. Her answers were not prompted in any way, and the tests were performed again the same day with the same results. I placed some importance on these findings because I have had occasion to observe them in two of Dandy's patients on whom bilateral section of the vestibular nerves had been performed. I was never able to get these responses again in my patient. A week later she did not experience the sensations, but when she opened her eyes after passive turning of her head, objects seemed to rotate in front of her.

While she was in the hospital hyperactive reflexes developed, and the Babinski test elicited a bilateral extensor response. It was felt that she had a tumor of the vermis, and a ventriculogram was made. The lateral ventricles were symmetrical and markedly dilated, but the third ventricle was not visualized. The findings, nevertheless, were considered sufficient evidence for a diagnosis of subtentorial tumor, and a cerebellar exploration was made. The cerebellum was normal. The vermis was incised so that the fourth ventricle could be viewed as high as the lateral recesses. The fourth ventricle was not dilated, and fluid and dye injected into the lateral ventricles failed to appear through the aqueduct. I believed that the patient could have a suprasellar cyst, a tumor of the third ventricle, a pinealoma or a tumor of the quadrigeminal plate; so the wound was closed. The patient improved, and the aqueduct was opened sufficiently to transmit fluid and dye. Two months later ventriculography was repeated. Clinically the patient had acquired a spasticity of the extremities that prevented her from walking. The complete ventriculogram on this second occasion revealed clearly a filling defect in the posterior aspect of the third ventricle, which led me to postulate a pinealoma (fig. 16).

The usual interhemispherical exploration was made. The pineal body was uninvolved, but when the tela choroidea was incised a vascular tumor was disclosed. Dilated vessels were apparently progressing in and out of the posterior wall of the third ventricle, and a plexus was seen coursing down into the sylvian aqueduct. Gentle tugging on this plexus markedly disturbed the patient's respiration, and though the vessels in view were cauterized, further hope of any operative benefit was abandoned. About six hours later the patient suddenly died of circulatory failure. Necropsy was denied, but in the light of the findings it was felt that the tumor may have arisen originally in the quadrigeminal plate and invaded the third ventricle secondarily. However, the tumor may well have had its origin in the choroid plexus, comparable to the tumor described by Dandy.<sup>27</sup> The smooth outline of the anterior border of the tumor as seen in the ventriculogram aroused my suspicion that it was partly cystic in nature. If this was so, I might have incised it when incising the tela choroidea, and then failed to recognize its true nature. A technical point is suggested here, that when the surgeon is exploring

27. Dandy,<sup>17</sup> p. 62.

## EXPLANATION OF FIGURE 17

Fig. 17 (case 17).—*A* is a ventriculogram demonstrating a filling defect in the posterior aspect of the third ventricle similar to one already shown (fig. 16). *B* is a diagrammatic representation of *A*. *F* indicates the foramen of Monro; *M*, massa intermedia; *T*, margin of filling defect due to a benign cyst of the third ventricle. *C* shows reconstructed drawings illustrating the position and relations of the cyst and the operative approach through the splenium of the corpus callosum. *C* indicates cyst; *G*, vein of Galen dividing into the smaller veins; *S*, divided splenium of the corpus callosum; *T*, incised tela choroidea. *D* is a photomicrograph of a cross-section of the cyst wall. *a* indicates the connective tissue capsule and *b* indicates the inner aspect of the cyst, composed of many layers of glial cells.

tissue in which fibers are fairly abundant. The cells are closely spaced in some areas, but they are rather uniform in size and no mitoses or giant cells are found. A few phagocytes near the inner surface contain brown pigment. There is no epithelial lining, nor is any colloid material present. The lesion appears to be a gliomatous cyst."

#### TUMOR OBSTRUCTING THE LATERAL AND THE THIRD VENTRICLE

CASE 18.—O. G., a white boy aged 8 years, was referred to the department of pediatrics by Dr. Robert Hughes, of Ottumwa, Iowa, in December 1936. For seven months the boy had complained of right frontal headaches, which recently had been accompanied by vomiting. For six months his left leg and arm had become progressively weaker. There was bilateral papilledema of 2 diopters, and the strength and deep reflexes on the left were markedly impaired.

A ventriculogram revealed a perplexing picture, but one which is accurate and worth while analyzing in retrospect. The left lateral ventricle was dilated and was shifted to the left. (Air had been injected into the left posterior horn.) Air progressed through the foramina of Monro, outlining a small portion of the third ventricle anteriorly and showing the margin of a definite filling defect. Only the anterior horn of the right ventricle was visualized (fig. 18). The tumor proved to be a cyst in the posterior aspect of the right frontal lobe. It yielded 30 cc. of clear yellow fluid, which contained 185 mg. of cholesterol per hundred cubic centimeters. A nonpedunculated mural nodule about the size of a walnut was situated in the mesial wall of the cyst in such a way as to block the right ventricle just posterior to the foramen of Monro; in addition, the nodule was compressing the posterior aspect of the third ventricle, producing the filling defect shown in the ventriculogram. The value of the study lies in the fact that filling defects in the third ventricle associated with filling defects in the lateral ventricles indicate tumors that are most likely not intrinsic in the third ventricle.<sup>28</sup> The tumor was extricated, and the patient made an uneventful recovery with complete return to normal.

#### TUMOR OF THE QUADRIGEMINAL PLATE

CASE 19.—C. H., a white girl aged 9 years, was referred to me in March 1936 by Dr. L. W. Chain, of Dedham, Iowa. When the child was 1 year old it was known that she had a divergent squint. She had always been unsteady when walking and had frequently fallen. She had grown markedly worse during the past six months, so that at the time of examination there was generalized hypotonia with a tendency to remain fixed in any relaxed position. When she was placed on her feet there was marked retropulsion. Her face was expressionless, and after some delay she would give short answers to questions in a rather explosive manner. The voice was bass and hoarse. There were divergent strabismus and fixation with either eye. The pupils were dilated and equal and reacted well to light. The deep reflexes were hyperactive, and all her extremities were ataxic to the usual cerebellar tests. There was astereognosis of the right hand. The intracranial tension was markedly increased so that the patient suffered severe headaches, had projectile vomiting and presented advanced bilateral papilledema.

A ventriculogram revealed ventricles that were markedly and symmetrically dilated (fig. 19A). A small amount of air was visible in the third ventricle, but

28. Dandy, <sup>17</sup> p. 72. Dandy,<sup>4</sup> p. 123. Reference should be made to the report of the thalamic tumor in case 15.

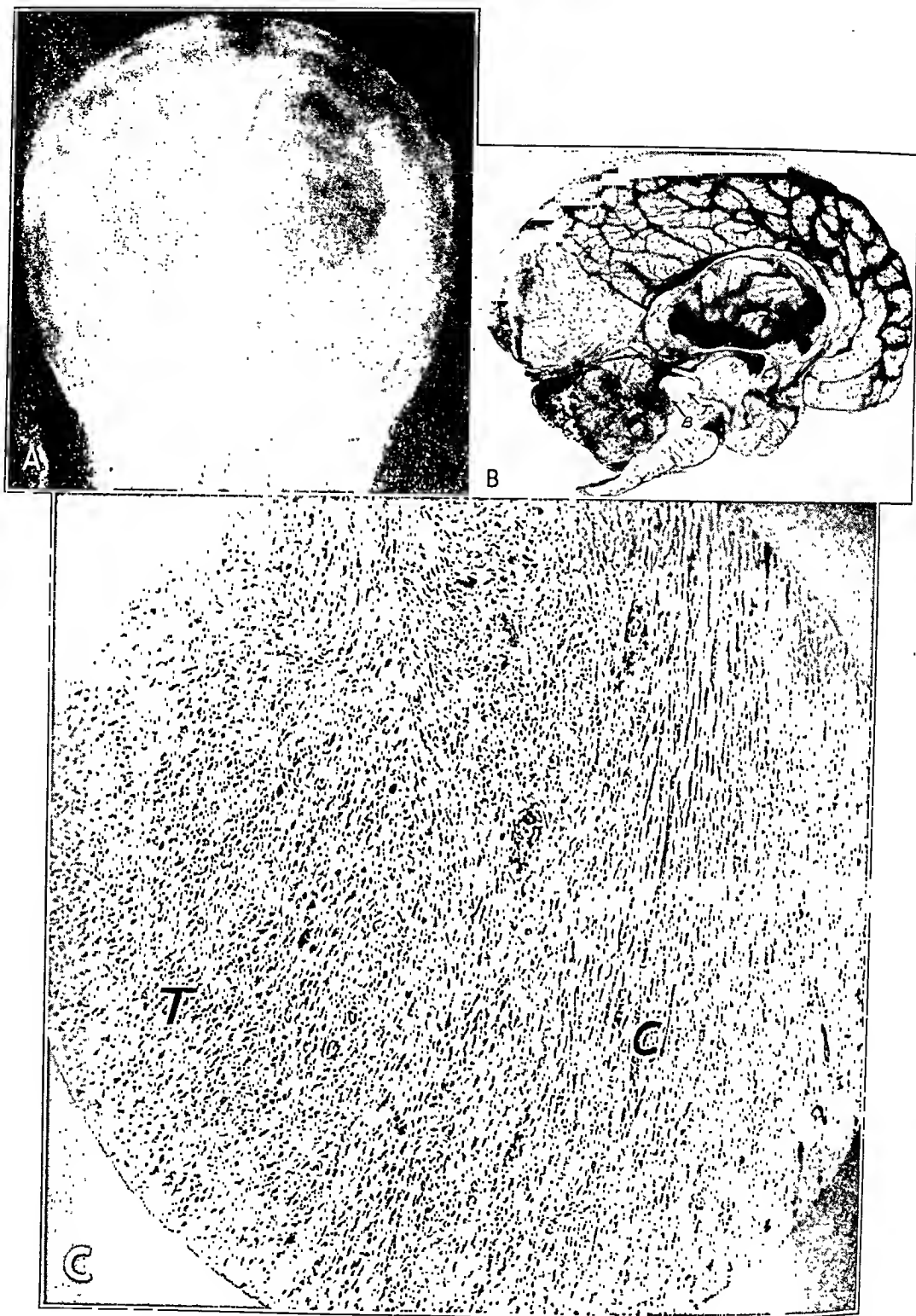


Fig. 19 (case 19).—*A* is a ventriculogram in the anteroposterior view, showing a small amount of air in the third ventricle. The lateral view failed to reveal a third ventricle shadow because the quantity of air injected was not more than enough to fill one lateral ventricle. *B* is a photograph of a brain demonstrating a dilated third ventricle. The appearance of a complete ventriculogram may be deduced from the photograph. I am convinced that if sufficient air had been injected, a more accurate deduction of the nature of the lesion could have been made. *T* indicates a tumor practically limited to the superior colliculi, and *B* indicates the margin of the operative defect from which a specimen for biopsy was obtained. Note the perforated septum pellucidum. *C* is a photomicrograph of the tumor, indicated by *T*, showing its pseudocapsule, *C*.

vermis, and the roof of the fourth ventricle was removed with it. The histologic appearance of the tumor was that of an astrocytoma, and the yellow fluid contained 120 mg. of cholesterol per hundred cubic centimeters. The patient recovered uneventfully, the disks receded and the pressure of the spinal fluid returned to normal and has remained so to the time of this report (six months). The patient now walks and performs the usual cerebellar tests normally.

CASE 22.—A. Ver D., a white boy aged 14, was referred to the department of pediatrics by Dr. P. M. Henry, of Prairie City, Iowa. For about one month

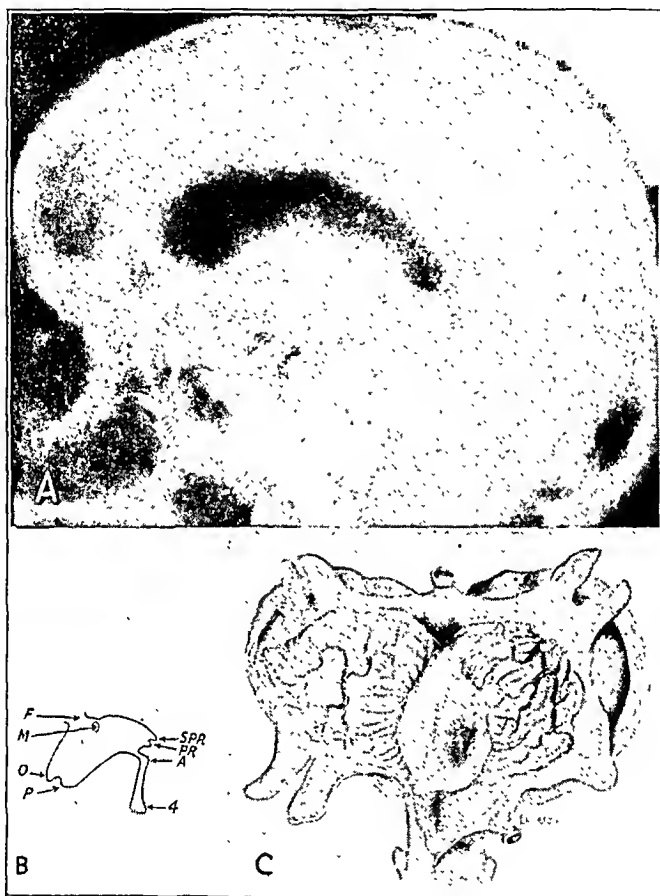


Fig. 20 (case 20).—*A* is a ventriculogram demonstrating a forward displacement of the fourth ventricle and the distal segment of the aqueduct of Sylvius. A sharp angular defect is produced in the upper segment of the aqueduct, which has proved to be constant with tumors in or pressing on the vermis cerebelli. The anatomic analysis of this angulation may be made (fig. 24 *B*). *B* is a diagrammatic representation of *A*. *F* indicates foramen of Monro; *M*, massa intermedia; *O*, optic recess; *P*, pituitary recess; *SPR*, suprapineal recess; *PR*, pineal recess; *A*, angulation of the aqueduct of Sylvius; *4*, compressed fourth ventricle. *C* is a drawing of the arachnoid (pial?) cyst disclosed at operation.

previous to admission there had been morning vomiting, and the patient complained of dizziness on sudden change of position of his head. He held his chin toward the left shoulder (fig. 22 *B*). His neck was stiff, and his right arm was ataxic.



cholesterol per hundred cubic centimeters. The tumor was extricated, and the patient recovered uneventfully. The circulation of the cerebrospinal fluid was restored to normal dynamics, the disks receded and the vestibular tests again revealed normal reactions.

CASE 23.—L. S., a white man aged 34, was referred to me in August 1935 by Dr. John I. Marker, of Davenport, Iowa. The patient complained of severe and almost continuous right frontal headache and dizziness, which had been present for eight weeks. For six days he had vomited almost everything ingested. On examination the vomiting was observed not to be projectile. The right arm had been amputated, but the left arm was slightly ataxic when the finger to nose test was performed. Examination of the eyegrounds showed only an old choroiditis. A lumbar puncture revealed a cytologically and chemically normal spinal fluid with an initial pressure of 8 mm. of mercury when the patient was in the prone position. The response to the Queckenstedt test was normal in every respect.

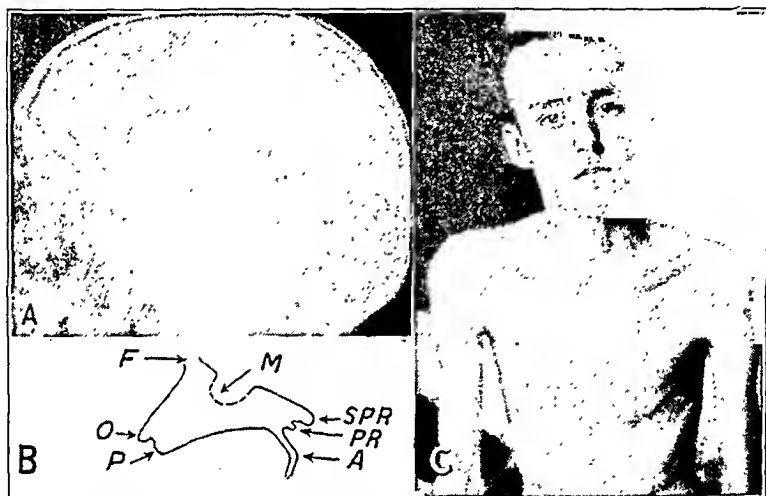


Fig. 22 (case 22).—*A* is a ventriculogram showing angular deformity of the aqueduct of Sylvius. *B* is a diagrammatic representation of *A*. *F* indicates foramen of Monro; *M*, massa intermedia; *O*, optic recess; *P*, pituitary recess; *SPR*, suprapineal recess; *PR*, pineal recess; *A*, angular deformity of the aqueduct due to a cystic astrocytoma of the vermis. *C* is a photograph of the patient showing the habitual posture of the head.

Two subsequent punctures revealed the same normal fluid dynamics. A striking and interesting feature revealed by the examination was a slow pulse rate which varied from 40 to 60 and a slow respiratory rate which varied from 8 to 20. The patient's family physician had noted the bradycardia for some weeks. Any cardiac condition was ruled out by the medical department.

A ventriculogram was made (fig. 23), but before air was injected into the ventricles a manometric reading of pressure in the dependent ventricle in the prone position was 180 mm. of cerebrospinal fluid. Though the anteroposterior view of the ventriculogram showed slightly dilated symmetrical lateral ventricles with some rounding of the angles, the consistently normal pressures were totally out of keeping with the clinical findings. The fourth ventricle had not been revealed, and since visualization of this ventricle was thought to be paramount to a complete

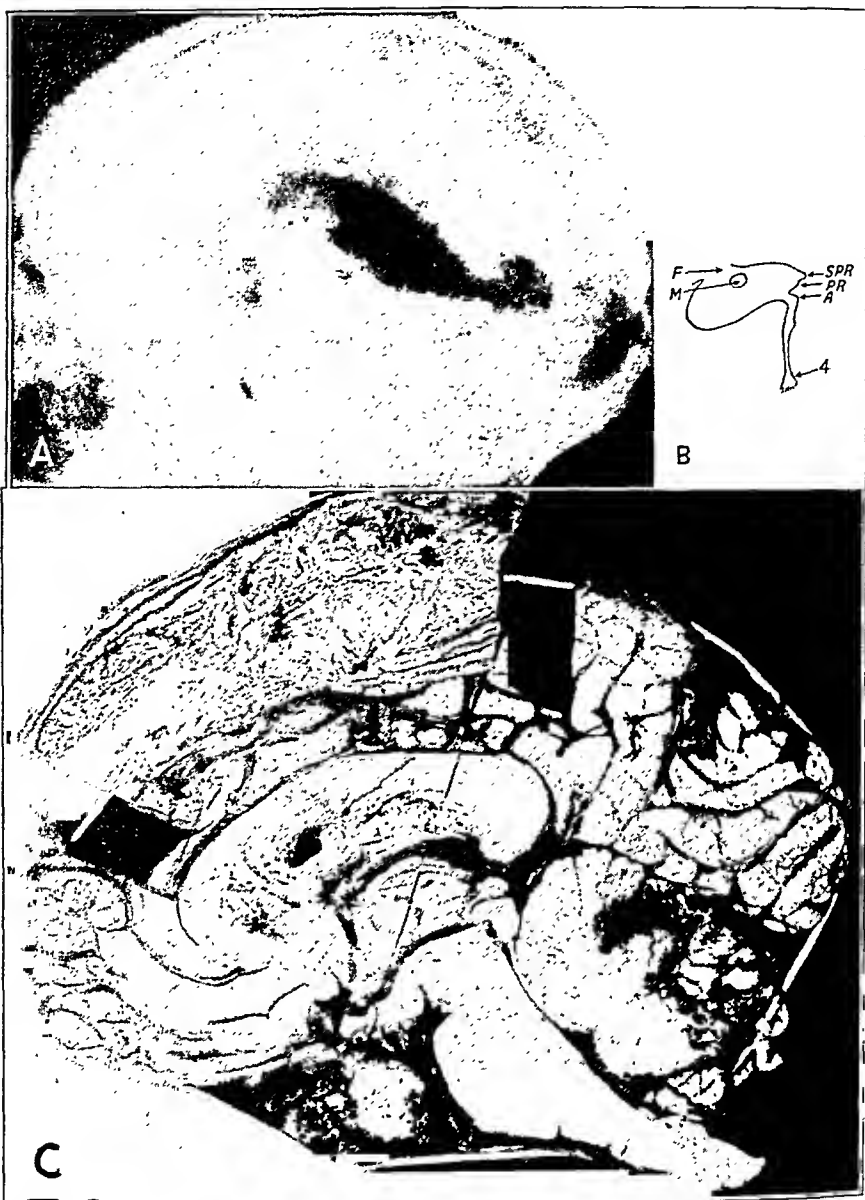


Fig. 24 (case 23).—*A* is a ventriculogram made with combined ventricular and spinal injections of air. There was a more complete filling of the aqueduct and fourth ventricle than previously shown (fig. 23). The obvious deformity here led to the recognition of the pathognomonic angular deformity in the upper segment of the aqueduct; this has proved to be of diagnostic value in subsequent cases. *B* is a diagrammatic representation of *A*. *F* indicates foramen of Monro; *M*, massa intermedia; *SPR*, suprapineal recess; *PR*, pineal recess; *A*, angular deformity of the aqueduct; *4*, compressed and anteriorly displaced fourth ventricle. *C* is a photograph of the brain. It may be seen that the angulation of the aqueduct is due to a buckling of the quadrigeminal plate which results from pressure directed anteriorly and superiorly. A portion of the tumor may be seen in the vermis. The greater portion was in the other half of the brain and was a cystic hemangioblastoma. Note the perforation in the septum pellucidum.

she had spells of vomiting without nausea, which lasted about a week and which occurred only at Christmas time each year. However, for the past year the patient had had severe morning headaches, often associated with intense vertigo, nausea and projectile vomiting. The vision had become blurred. Aside from marked bilateral papilledema, the neurologic examination gave entirely negative results.

A complete ventriculogram revealed symmetrically dilated lateral ventricles, with an equivalent dilatation of the third and fourth ventricles (fig. 27). An



Fig. 25 (case 24).—*A* is a ventriculogram revealing a dilated proximal segment of the aqueduct with visualization to the point of obstruction. *B* is a diagrammatic representation of *A*. *F* indicates foramen of Monro; *M*, massa intermedia; *SPR*, suprapineal recess; *PR*, pineal recess; *AS*, aqueduct of Sylvius to the point of obstruction. *C* is a photograph of the brain showing the dilated aqueduct indicated by *AS*. The tumor completely obstructed the aqueduct at the plane of section through the brain stem. This precluded the usual angular deformity of the aqueduct.

obstruction of the foramen of Magendie was postulated, and a subtentorial exploration revealed the dura to be slightly adherent to the cerebellar cortex by cobweb-like arachnoid adhesions. The cerebellar tonsils were herniated beneath the atlas,

necessitating a removal of its arch. When this was done a gush of fluid came from the spinal arachnoid space. When the tonsils were separated, the foramen of Magendie was found to be obstructed by adhesions except for an opening the size of a tiny pin. The opening was enlarged, bringing a dilated fourth ventricle into view. From a prognostic standpoint, it should be kept in mind that the obstruction may be even distal to the cerebellar cistern, namely, in the basal cisternae. This patient, nevertheless, made a striking recovery, with recession of the papilledema and restoration of the spinal fluid pressure to within normal limits. She has remained in this state of recovery for the past year.

#### SUMMARY

An opinion concerning the advantage and use of pneumography is given, based largely on my experience. Time and experience have proved that ventriculography is a safe procedure and indispensable to the diagnosis and localization of many tumors of the brain. To obtain the maximum advantage, however, each patient must be treated individually and certain time-tried policies must be strictly observed. It is felt that ventriculography has not yet reached its fullest measure of usefulness, because of illogical and ill founded fear of its application. Its safety and usefulness have been proved, so that now it is only logical to extend its application and incorporate the method of precision whenever it can possibly provide added information of surgical importance. To this end I have given evidence to show that even when the neurologic examination in certain cases has provided data of positive value, a preliminary ventriculogram may be of decided value in planning the optimum method of operative attack. This feeling seems to be contrary to the opinion universally expressed in the literature. It is not in any way proposed that the neurologic examination should not be used to the fullest extent of its resources. However, advances in technical neurosurgery and increasing courage to tackle more serious problems demand that localization be more accurate than neurologic examination can at all times guarantee.

In addition to the more extended application of ventriculography, I have in a few cases found combined ventricular and spinal injection of air helpful and unattended by danger if the intracranial pressure has been relieved.

Moreover, it is advocated that injections of air be complete, particularly in view of localizing tumors in and about the third ventricle, aqueduct and fourth ventricle. Wide variance in operative exposures makes accurate localization here a *sine qua non*. Cases have been presented to illustrate the possibility and plausibility of obtaining complete ventriculographic information.

#### CONCLUSIONS

1. Ventriculography has a broader application for the surgeon than is probably yet utilized.

## ETIOLOGIC FACTORS OF MESENTERIC LYMPHADENITIS

JAY IRELAND, M.D.

CHICAGO

Mesenteric lymphadenitis is an old subject. Bertein and Worms<sup>1</sup> stated that Sydenham in 1723 was the first to describe enlargement of the mesenteric glands in children. Numerous excellent papers have been written on this subject since then describing the pathologic picture, symptoms, diagnosis and treatment. However, the etiology has always been a questionable factor. It was because of this indefinite etiology that this study was undertaken. An attempt has been made to determine the etiologic significance of the various theories previously advocated and also to advance some new ones.

This report is based on a series of twenty-two patients in whom mesenteric lymphadenitis was found at operation at the Children's Memorial Hospital from the years 1931 to 1936 inclusive. Appendectomy was performed on all but two. The appendixes were not removed from these two because intussusception was present in one and intestinal hemorrhages had preceded the operation on the other. The ages of the patients ranged from 2 to 13 years inclusive. There were twelve boys and ten girls. The mesenteric glands varied in size from some that were slightly larger than a pea to a mass the size of a lemon in one case. Intestinal obstruction from the enlarged glands, as reported by Wantoch<sup>2</sup> in two patients, was not observed in this series. Twenty-one of the twenty-two patients recovered, and one died of streptococcic peritonitis due to the rupture of a suppurative gland.

In this report the theories as to the direct agent causing mesenteric adenitis will first be considered, and then the manner of entrance of this agent into the glands will be advanced.

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Read before the Chicago Surgical Society, Feb. 5, 1937.

From the Surgical Service of Dr. A. H. Montgomery at the Children's Memorial Hospital.

1. Bertein, P., and Worms, G.: *Les adénopathies du mésentère*, *Gaz. d. hôp.* **82**:1291-1295, 1909.

2. Wantoch, H.: *Ueber tiefsitzende Duodenalstenose infolge atuberkulöser oder tuberkulöser Lymphdrüenschwellungen der Mesenterialwurzel*, *Deutsche Ztschr. f. Chir.* **226**:135-139, 1930.

the outer muscular layer. In one area there was a large portion of autolyzed mucosa. Similar changes were found in the small section of the ileum. A Gram stain failed to reveal organisms in the intestinal wall.

Similar cases of purulent abscess formation from necrotic mesenteric lymph glands have been described previously by Nyström,<sup>11</sup> Pólya and von Navratil,<sup>12</sup> Borchard,<sup>13</sup> Doyen,<sup>14</sup> Johnsson-Breuer<sup>15</sup> Wilensky and Hahn,<sup>3</sup> Etchegorry<sup>16</sup> and Calvanico.<sup>17</sup>

Head<sup>18</sup> reported a case of tuberculous mesenteric lymphadenitis in which secondary infection and rupture occurred. He found two similar cases reported in the literature.

Attempts to find organisms in the glands removed at operation have usually been unsuccessful. Wilensky and Hahn<sup>3</sup> found a gram-negative bacillus in the abdominal fluid of one patient and recovered *Str. haemolyticus* from a suppurative gland of another. Marshall<sup>19</sup> cultured the glands of an unstated number of his forty-eight patients and found *B. coli* in two instances. Goldberg and Nathanson<sup>20</sup> found *Str. haemolyticus* in the glands of one of eight patients. Heusser<sup>21</sup> examined the glands of twenty-five of his patients and found *B. coli* in only two. In the present series, *Str. haemolyticus* was cultured from a lymph gland of the patient who died.

Strömbeck<sup>22</sup> found mesenteric lymphadenitis associated with paratyphoid infection in a patient on whom he operated.

11. Nyström, G.: Studier öfver resultaten af behandling för appendicit vid akademiska sjukhuset i Uppsala (kirurgi), *Nord. med. Ark. (supp.)* **7**:1-258, 1907.

12. Pólya, E., and von Navratil, D.: Untersuchungen über die Lymphbahnen des Wurmfortsatzes und des Magens, *Deutsche Ztschr. f. Chir.* **69**:421-456, 1903.

13. Borchard, A.: Die primäre Lymphangitis des Wurmfortsatzes, *Deutsche med. Wchnschr.* **54**:1074-1075 (June 29) 1928.

14. Doyen, cited by Strömbeck.<sup>22</sup>

15. Johnsson-Breuer, cited by Strömbeck.<sup>22</sup>

16. Etchegorry, P. A.: Linfadenitis mesentérica supurada, *Semana méd.* **1**: 990-993 (April 21) 1927.

17. Calvanico, R.: Le modificazioni dell'apparato linfo- adenoideo locale dell'appendicite, *Policlinico (sez. chir.)* **34**:253-275 (June) 1927.

18. Head, J. R.: Tuberculosis of the Mesenteric Lymph-Glands, *Ann. Surg.* **83**:622-633 (May) 1926.

19. Marshall, C. J.: Simple Ileo-Caecal Lymphadenitis, *Brit. M. J.* **1**:631-632 (April 14) 1928.

20. Goldberg, S. L., and Nathanson, I. T.: Acute Mesenteric Lymphadenitis: Clinical Syndrome in Children Simulating Appendicitis, *Am. J. Surg.* **25**:35-40 (July) 1934.

21. Heusser, H.: Die Schwellung der mesenterialen Lymphdrüsen, *Beitr. z. klin. Chir.* **130**:85-98, 1923.

22. Strömbeck, J. P.: Mesenteric Lymph-Adenitis: A Clinical Study, *Acta chir. Scandinav. (supp. 20)* **70**:1-254, 1932.

writers, such as Struthers,<sup>7</sup> McFadden<sup>32</sup> and others. Bell<sup>33</sup> stated that the condition should be considered as tuberculous until proved otherwise. McFadden<sup>32</sup> thought that the tuberculosis was probably bovine in type. While there is no doubt that there are cases of mesenteric lymphadenitis due to tuberculosis, they represent a small minority at the present time.

Strömbeck<sup>22</sup> removed the glands of fourteen patients, and those of four were proved to be negative for tuberculosis on inoculation of guinea-pigs. Heusser,<sup>21</sup> by means of cultures, the sodium hypochlorite test and inoculation of guinea pigs, apparently proved the absence of tuberculosis in his forty patients. Freeman<sup>4</sup> removed glands from fifty patients, and those of forty-three proved to be negative for tuberculosis. In ten cases inoculation of guinea pigs were made, and evidence of tuberculosis was found in only four. Strömbeck<sup>22</sup> made a roentgenographic examination of the abdomen for calcified lymph glands in thirty patients from twenty months to nine years after operation, with negative findings for tuberculosis. In 85 per cent of his forty patients he ruled out tuberculosis with as great a degree of certainty as clinical examination admitted.

A tuberculin test was made on eight patients in the present series, and a negative reaction was uniformly found.

Lewis<sup>34</sup> suggested that *Bacillus melitensis*, the causative organism of undulant fever, might be an etiologic factor. However, Davison<sup>35</sup> stated that in undulant fever the white blood count is reduced or is normal. In twenty-one of the twenty-two patients in the present series, the leukocyte count ranged from 4,600 to 26,500 per cubic millimeter of blood. In seventeen, the count ranged from 10,200 to 26,000, which was considered above normal; in three, it ranged from 7,500 to 10,000, which was considered normal, and in one, it was 4,600, which was considered indicative of leukopenia. Such blood pictures militate against the conception that *B. melitensis* was the causative organism in all cases.

In addition, cultures of the urine of four patients and of the stools of two were made for *B. melitensis*, and all were negative. Agglutination tests with *B. melitensis* and the patient's blood were also made on two patients, and the results were the same. From these observations it would seem evident that *B. melitensis* is hardly worth considering as a causative agent.

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32. McFadden, G. D. F.: Mesenteric Lymphadenitis and Its Clinical Manifestations, with Special Reference to Its Differential Diagnosis from Appendicitis, *Brit. M. J.* 2:1174-1177 (Dec. 24) 1927.

33. Bell, L. P.: Mesenteric Lymphadenitis Simulating an Acute Abdominal Condition, *Surg., Gynec. & Obst.* 45:465-473 (Oct.) 1927.

34. Lewis, Dean, cited by Freeman.<sup>4b</sup>

35. Davison, W. C.: Brucellosis, *Bull. Chicago Med. Soc.* 38:552 (March 21) 1936.

substance alone. It is not until an animal becomes refractory to the gonadotropic substance that cyst formation begins to result from the continued injection of estrogen.

The application of these observations to human beings deserves emphasis. As is well known, all forms of chronic cystic mastitis are much less common in multiparous than in nonparous women, and it is not uncommon for the disease to regress during pregnancy and lactation. In two women recently seen in Johns Hopkins Hospital complete symptomatic cure of chronic cystic mastitis occurred during the first half

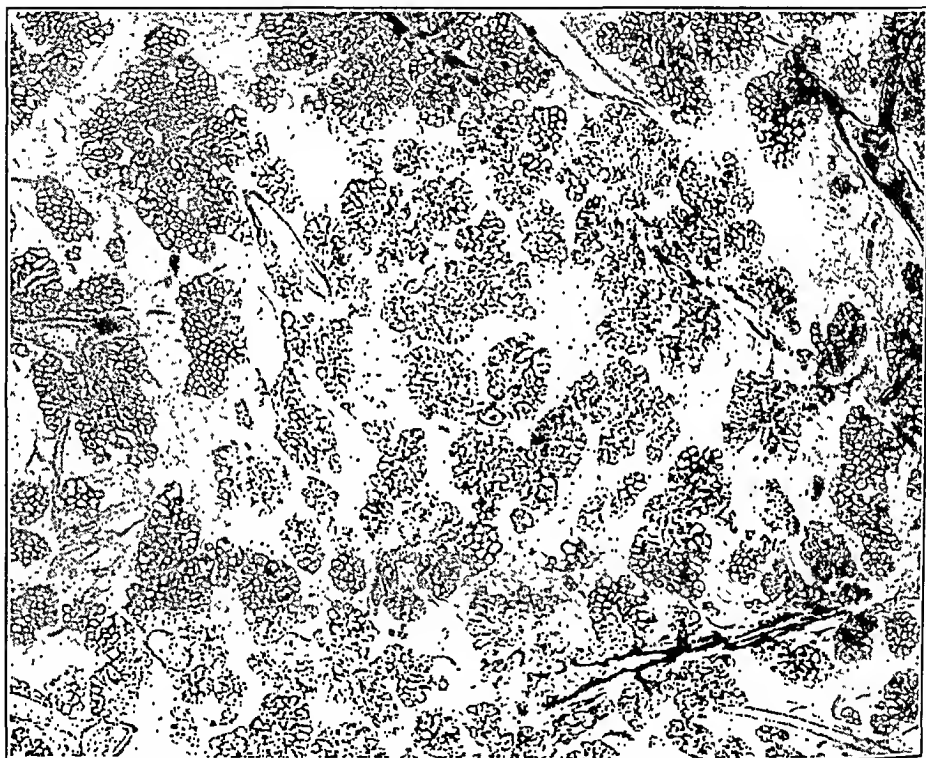


Fig. 16.—Paraffin section ( $\times 18$ ) of a mammary gland from an intact female rat treated from the twenty-first day of life with 200 micrograms of estrogen daily for eighty-one days, together with 50 rat units of gonadotropic substance from the urine of pregnant women daily. The gland shows lobular growth which has partially regressed, but the cystic changes which would have been expected from the high doses of estrogen have been prevented. Compare with figures 7 to 11, which show changes that result from administration of estrogen alone.

of the period of pregnancy.<sup>19b</sup> The artificial induction of the mammary changes of pregnancy would be effective treatment for chronic cystic mastitis in the human being.

<sup>19b</sup> Lewis, D. L., and Geschickter, C. F.: Endocrine Therapy in Chronic Cystic Mastitis, *J. A. M. A.* **109**:1894 (Dec. 4) 1937.



extension and increased branching of the ducts, the result being a type of gland normally seen in the female adult. Stimulation of the testis or administration of androgen produces an effect very different from that of estrogen, causing the development of the peculiar, lobule-like structures characteristic of the normal adult male. The human male mammary gland also presents a typical structure consisting of thick, poorly branched ducts lined by several layers of epithelium and enmeshed in a dense fibrous matrix. The excessive mammary development sometimes seen at or soon after puberty and the rarely seen bilateral gynecomastia accompanying tumors of the adrenal cortex possess a similar architecture. It is possible that this hypertrophy results from the action of androgen, as both the maturing testes and hyperactivity of the adrenal cortex are apparently responsible for gynecomastia observed clinically. It has been shown that estrogen will also cause enlargement of the human male breast. However, in a great many cases gynecomastia is unilateral and must be ascribed to some inherent factor in mammary response independent of an endocrine abnormality. When testosterone is administered for long periods to rats, there are a great increase in the epithelium lining the ducts and alveoli and considerable shedding of cells into the lumens of these structures. Figures 17 and 18 show the gross and microscopic structure of a mammary gland of a female rat treated from birth with 250 micrograms of testosterone propionate given daily for forty-two days.

Vest (personal communication), at the Brady Urological Institute of the Johns Hopkins Hospital, has treated a series of eight patients over periods of from three months to a year with injections of testosterone propionate. The patients received doses varying from 50 mg. weekly to 10 mg. daily, the ages being  $3\frac{1}{2}$ , 9, 23, 27, 31, 32, 33 and 62 years, respectively, at the beginning of treatment. Although all of these patients showed development of the external genitalia and of the prostate, none of them showed any evidence of mammary enlargement. One patient, a 31 year old man, had slight tenderness beneath one nipple and some increased density of fibrous tissue at one examination. This had disappeared, however, one week later and did not recur, despite continuation of the treatment. Kenyon and others<sup>24</sup> in four cases of gynecomastia found normal excretion of estrogen in the urine, but the androgen in the same cases varied from none to normal amounts. One of us (C. F. G.) has performed biopsies in three cases of gynecomastia before and after injections of testosterone in doses ranging from 50 to 150 mg. without observing significant mammary changes.

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24. Kenyon, A. T., and others: Urinary Excretion of Androgenic and Estrogenic Substances in Certain Endocrine States, *J. Clin. Investigation* **16**:705, 1937.

## PITUITARY LACTOGENIC SUBSTANCE

It is now definitely established that the actual secretion of milk is under the control of a principle of the anterior lobe of the pituitary gland. A question still to be answered concerns the nature and the extent of the histologic change that is brought about by this substance. More study with the use of potent pituitary substances is necessary



Fig. 19.—Whole mount ( $\times 27$ ) of a mammary gland of a female castrated at the age of 21 days and treated with 100 micrograms of estrogen daily for twenty days followed by administration of 40 bird units of pituitary lactogenic substance daily for five days. The terminal buds, having been rendered abnormal by the administration of estrogen, are diffusely and irregularly distended with secretion.

to determine the effect of the lactogenic substance on the mammary structure.

The secretory changes which follow high doses of estrogen are in part the result of hypermaturation of mammary epithelium and are probably

These abnormal changes are histologically very similar to certain diseases of the human breast, and it is interesting to make a comparison when one is studying human material. However, it must be emphasized that there is no proof that a correlation exists between these mammary changes in the rat and those seen in the human being, and these experiments in no way prove that the mechanisms involved are the same. One can only say that a comparison makes it appear probable that these benign lesions of the human breast are in part of endocrine origin. In addition to other variations due to difference in species, the human mammary gland differs from those of all other species in its dense and abundant fibrous stroma. To this unique structure the human breast owes its external form, and it is this tissue which enters into the formation of many of the benign tumors of the breast. Because of this marked difference between the mammary gland of the human being and that of the experimental animal, little profitable correlation can be made between the changes in connective tissue observed in animals and those seen in human beings. It is probable, however, that in the rat and in the human being the loose areolar periductal connective tissue makes a similar response, while the dense stroma of the human breast has no counterpart in the rat, its place being taken by the loose fatty tissue into which the mammary tree of the rat ramifies.

#### SUMMARY AND CONCLUSIONS

A study has been made of mammary abnormalities in the rat resulting from the administration of a variety of endocrine substances, including estrogen, testosterone, progesterone and anterior pituitary substances. A comparison between these pathologic states and similar diseases of the human breast has been attempted. The following observations and conclusions may be made:

1. There is a distinct variation in histologic picture and in physiologic response in different portions of the mammary gland. These histologic differences are accentuated by growth stimuli and contribute to the pathologic picture of induced mammary lesions.

2. The mammary glands of males and females differ in their structure and in their inherent ability to respond to stimuli. These differences are entirely independent of the testis or ovary, as shown by early castration, and are therefore classed as genetic sexual differences.

3. These variations in different glands and in different portions of the same gland show that a large part of any pathologic mammary state has its origin in the gland itself and is independent of abnormal endocrine influences.

4. Administration of large doses of estrogen to rats for varying periods results in a variety of changes which simulate that group of

# INGUINAL HERNIOPLASTY WITH FASCIA TRANSPLANT

BRUCE L. FLEMING, M.D.

PHILADELPHIA

Herniorrhaphy of any type has been found in all clinics to be an inadequate procedure for the treatment of some inguinal hernias. Recognition of this fact has led the most recent workers on this particular problem to seek some method that will effect a larger percentage of cures. Resulting methods in almost every instance comprise the use of fascia either as a suture material or for plication in the abdominal structures or in the form of a transplant.

In a search for reasons for recurrent or postoperative inguinal hernia, it is well to recall some anatomic conditions of the inguinal region. An indirect inguinal hernia has its exit from the abdominal cavity through the internal ring—an opening in the transversalis fascia. A direct inguinal hernia protrudes through the floor of the canal or else bulges this structure. It then becomes the first covering of such a hernia. All inguinal hernias, therefore, either pass through or push before them the transversalis fascia. These facts need emphasis. The transversalis fascia should be considered the first line of defense in the repair of an inguinal hernia. It is similar to fascia found elsewhere in the body, though it is thinner than other such tissue in the inguinal region. Fibrous tissue is known to be the best tissue for the application of a transplant of fascia, but its importance in this respect has not been generally recognized.

The spermatic cord in the inguinal region is in direct contact with the transversalis fascia and is attached to it by the fibers of the cremaster muscle. These fibers must be freed and retracted with the cord for complete exposure of the floor of the inguinal canal. This procedure is also necessary to repair the internal inguinal ring completely. Any method of herniorrhaphy, therefore, that does not include mobilization of the spermatic cord cannot allow effective repair of the internal ring or repair and reenforcement of the floor of the canal.

Inguinal hernia of the congenital type, such as is found in children and some adults, may be repaired successfully by high ligation of the sac, transplantation of the stump and suture of the internal oblique muscle to the fascia reflected from Poupart's ligament.

Eberts and Hill,<sup>4</sup> reported in 1914, demonstrated that the smooth external surface of a transplant of fascia heals best when sutured closely in contact with other tissues. Such a flap, therefore, should be so turned that the surface of the muscle is outward. They found that a free flap of fascia when sutured heals without reaction or diminution in size. They furthermore pointed out that gentle handling of tissues and strict asepsis must be practiced in order to get such results.

Gallie and LeMesurier<sup>5</sup> in 1921, from animal experimentation, found that the edges of incised fascia heal by means of cells from the attached areolar tissue. Such healing is not firm. This prompted them to practice and recommend the removal of all areolar tissue and the scarification of muscle and the overlapping of fascia in repair. These investigators later found that a fascial suture becomes a permanent part of the tissue in which it is used. Other experimental work done on animals by Koontz,<sup>6</sup> and first reported in 1926, demonstrated that fascia lata and inguinal ligament, if cleaned of all areolar tissue and coapted, unites firmly by the growing together of the connective tissue fibers of each. The strength of such healing was found to depend on the intimacy of contact of the fibrous components and was referred to as fascia to fascia healing. Koontz therefore recommended tight sutures in transplantation of fascia. Other work with such transplants or sutures has been in the repair of hernia in man.

Thus one finds ample experimental evidence to prove that a transplant of fascia heals firmly when freed of all areolar tissue and fat and completely severed from its blood supply, provided it is closely and firmly sutured under strict aseptic conditions with the smooth surface in contact. Scarification of muscle before suturing results in firmer union with fascia, and surgeons of experience do not hesitate to accept this experimental finding, for they are aware that it is in keeping with clinical results.

#### HERNIOPLASTY

Mann<sup>7</sup> reported the use of transplants in the repair of hernia. His method, similar to that of Kirschner, consists of the application of the transplant ventral to the internal oblique muscle. He recommended suturing such a flap slightly "on a stretch," though reasons for this have not been demonstrated experimentally.

4. Von Eberts, E. M., and Hill, W. H. P.: Free Transplantation of Fascia, *Surg., Gynec. & Obst.* **18**:318-321, 1914.

5. Gallie, W. E., and LeMesurier, A. B.: The Use of Living Sutures in Operative Surgery, *Canad. M. A. J.* **11**:504-513, 1921.

6. Koontz, A. R.: Experimental Results in the Use of Dead Fascia Grafts for Hernia Repair, *Ann. Surg.* **83**:523-536, 1926.

7. Mann, A. T.: New Methods of Operating for Difficult Herniae, *Journal-Lancet* **37**:331-337, 1917.

cross the crease of skin in the groin. The flap of skin and subcutaneous tissue is reflected upward, exposing the aponeurosis of the external oblique muscle, which is incised ventral to the spermatic cord. This incision is prolonged laterally beyond the internal ring and medially through the external ring. The aponeurosis is separated from the underlying structures and freed of fat and areolar tissue by the use of dry gauze. The fibers of the cremaster muscle are separated with blunt scissors when an indirect hernia is being repaired. The sac is located, isolated and opened. High ligation is done with a transfixing suture, and at least a part of the excess sac is plicated and made to fit snugly around the cord dorsal to the internal oblique muscle and cephalic to the internal ring. It is sutured in this position. Double sacs are sought and, when found, are converted into one sac. The spermatic cord with the cremaster muscle is freed from the inguinal ligament and the transversalis fascia. All fibers of this muscle, fat and areolar tissue are removed from this fascia. In the operation for direct hernia the sac is opened, its edges are sutured from within and overlapped and may be transplanted under the internal oblique muscle or allowed to retract in the abdomen. The transversalis fascia is sutured so that its edges and the sac are buried. Overlapping of the transversalis fascia necessitates complete removal of fat and areolar tissue from its under-surface if firm union is to result. Since this is a rather difficult technical procedure, suture by inverting the edges is practiced. The internal ring is snugly sutured so as barely to emit the cord without interfering with its circulation. To accomplish this, the internal oblique muscle must be retracted rather severely. The lower flap of skin and subcutaneous tissue is freed laterally from the fascia covering the muscles of the thigh and retracted. Exposure may be increased by extending this incision cephalically. A transplant of sufficient size to cover the inguinal floor is removed from the fascia lata just caudad and somewhat dorsal to the anterior pubic spine. Bleeding vessels are carefully clamped and ligated, and a gauze sponge is placed there to control oozing. The corners of the transplant are picked up with small hemostats, carefully freed of fat and areolar tissue, inverted and sutured to the transversalis fascia with a continuous suture of no. 00 chromic catgut. This part of the operation requires careful technic, but by first suturing the corners of the transplant, the procedure is facilitated. A few firmly tied single stitches are used for close coaptation. The lateral corners of this flap are sutured above and below the cord. These sutures coapt the transplant with the internal ring, which procedure is particularly important when a large indirect hernia is being repaired.

The operation is continued by suturing the conjoined tendon and internal oblique muscle to the inguinal ligament with interrupted sutures of no. 1 chromic catgut. These sutures are so placed that the muscular fibers are not separated.

If there is marked deficiency of the conjoined tendon, a triangular flap from the sheath of the rectus muscle is turned down and sutured to the underlying structures.

The flaps of the fascia of the external oblique muscle are overlapped slightly and sutured dorsal to the cord. Gauze is removed from the exposed area of the thigh, which is carefully inspected for bleeding. Strict hemostasis in this area is very important. The skin flaps are closed without drainage with nonabsorbable sutures. Dressings are secured by long strips of adhesive tape so placed as to give pressure over the part of the thigh from which the transplant was taken. A separate incision below the iliac spine, for the purpose of securing a suitable transplant of fascia, is rarely necessary.

The following details in technic are important: careful preparation of the skin, strict asepsis, strict hemostasis and removal of all fat and areolar tissue from

a temperature of 102.2 F. Physical examination gave entirely negative results, save for some mild reaction in the wound. I believe that there was infection of the transplant, which resulted in its destruction rather than in the formation of an abscess. Six months after operation a postoperative direct hernia was discovered on examination. The recurrence is attributed to infection.

CASE 3.—M. M., aged 22, was admitted to the hospital for repair of a large indirect inguinal hernia. Operation was carried out with the patient under ether anesthesia. The tissues were fairly well developed. A large hematoma appeared in the thigh and in the inguinal region a few hours after operation. The incision in the skin was opened, and some clots were removed daily for several days. I believe that the transplant was absorbed or else lost with some of the clots. The patient returned to work five weeks after discharge. Postoperative hernia of the direct type was found on examination four months later. This case was one of the earliest in which this operation was used, and recurrence is attributed to hemorrhage resulting from poor technic.

CASE 4.—M. K., aged 48, had bilateral indirect inguinal hernia, the right hernia being in the scrotum. Operation was done with the patient under ether anesthesia, and a saddle-bag sac was found. The internal oblique muscle was so markedly atrophied that it was of little use in repair. The internal ring was very large. Pulmonary complications developed postoperatively and also an infection of the operative wound, which resulted in the formation of an abscess and sloughing of the transplant. The patient returned to work as a janitor as soon as he was discharged from the hospital. A postoperative hernia of the indirect type resulted about ten months later.

#### CONCLUSIONS

The tissues in the inguinal region are inadequate for the repair of hernia in some patients.

The transversalis fascia should be considered the first line of defense in repair.

Mobilization of the cord is necessary for repair of the transversalis fascia, particularly of the internal ring.

The floor of the inguinal canal (transversalis fascia) is the best place for the application of a transplant of fascia.

Fascia for transplantation may be taken from the fascia lata through an incision made for repair of the hernia.

Strict asepsis and careful hemostasis are most important in the transplantation of fascia. Infection and hemorrhage were the causes of the failures in the reported cases.

This series of cases represents the group of inguinal hernias in which the incidence of recurrence is highest.

In the florid stage the zones of ossification of all the bones, including the vertebrae but excepting the flat bones of the skull, show an increase in width in the cartilage plates. The cartilage does not show the normal regularly progressive zone of ossification, but instead its advance is irregular and disorderly, with uneven lines being left behind in the epiphyses and diaphysis. Small nuclei of bone are seen distributed through the cartilage. As growth proceeds, these points coalesce, giving the main nucleus a ragged contour. The malacic changes result in humerus varus, coxa vara and genu valgum. On the concave side the periosteum is thickened with the formation of osteophytes; on the convex side the cortex is thin. The vertebral bodies are flattened, and the anterior margins are pointed or tongue shaped along the inferior border. The kyphosis is usually due to wedging between the lower two thoracic vertebrae. The sacral segments usually remain unfused. In the stage of healing there is consolidation of the irregular islands of ossification, but the shape is never completely normal. The ends of the long and short bones are enlarged and flattened. Roentgenologic examination of the hips reveals small femoral heads with short necks in coxa vara in relatively large acetabulums. The vertebrae are plateloid.

#### POLIOMYELITIS

*Immunity and Portal of Entry in Poliomyelitis.*—Toomey<sup>2</sup> discusses the confusing and complicated reports on experimental immunization against poliomyelitis. He believes that neutralizing antibodies (humoral) are a good index of immunity. Contrary opinions, he believes, are due to the fact that experimentally the disease is not introduced through the natural portal of entry. He believes that the natural portal is the gastrointestinal tract and that the virus is absorbed there and spreads along the sympathetic and parasympathetic chains to the lumbar, cervical or bulbar area. The usual spread, he believes, may be prevented by free cholesterol in the intestine or even by cholesterol in the white nerve fibers.

#### CHRONIC ARTHRITIS

*Fever Therapy for Arthritis.*—Simmons and his co-workers<sup>3</sup> studied the value of fever therapy for the arthritides, using the Kettering hypertherm in 81 cases. In 23 cases of gonorrheal arthritis 82 per cent of the patients were cured or markedly improved after twenty-six hours of fever with a temperature between 106 and 107 F. They believe that a minimum of twenty-five hours of fever is necessary before one con-

2. Toomey, J. A.: Active and Passive Immunity and Portal of Entry in Poliomyelitis, J. A. M. A. **109**:402 (Aug. 7) 1937.

3. Simmons, E. E.: Am. J. M. Sc. **194**:170, 1937.



made by repeatedly making roentgenograms, which show a marked tendency to spontaneous healing in this form of osteitis.

[ED. NOTE.—If there is any question of neoplastic metastases it is often better to perform a biopsy than to wait for roentgenologic evidence of changes.]

*Infection of the Spinal Epidural Space.*—Browder and Meyers<sup>7</sup> present 7 case histories of spinal epidural infection and discuss this clinical entity. They believe that it is frequently missed clinically and the osteomyelitic involvement of the vertebrae overlooked at autopsy. The condition was acute in 5 of their cases and chronic in 2. Clinically the patients with acute attacks give a history of previous infection, boring pain in the spine, radicular pain and involvement of the spinal cord. When the infection is chronic the syndrome is not so definite, although these same features, to a less degree, usually occur. They believe that the condition comes from an infection adjacent to the vertebral column or by a hematogenous route from a more remotely situated focus, such as acute infection of the upper part of the respiratory tract, otitis media, tonsillitis, furunculosis, phlebitis, puerperal sepsis or infection of the urinary tract. Infections of the latter type are characterized by a zone of metastatic vertebral osteomyelitis. The cases reported presented, besides the spinal epidural infection, 2 instances of osteomyelitis in the cervical region, 2 in the dorsal region, 1 in the lumbar region, 1 in the head of the sixth rib and 1 in an unknown site.

*Disturbance of Growth Resulting from Osteomyelitis.*—Siegling<sup>8</sup> reviews 423 cases of osteomyelitis seen at the University of Chicago Clinics. Two hundred and forty-one of these were instances of involvement of the long bones in children. In 4.9 per cent there was increase in the length of the long bones, and in 31.5 per cent there was an arrest of growth; included in this group were 79 instances of suppurative arthritis of the hip joint. The author warns against trauma to the epiphysis in operative procedures for osteomyelitis, stressing particularly that the periosteum should not be stripped from the cartilage near the epiphysis. Parents whose children have had osteomyelitis of the long bones should be warned of the frequent occurrence of deformity.

*Osteomyelitis of the Long Bones and Typhoid Fever.*—Moiroud<sup>9</sup> reviews the history of typhoid osteomyelitis. Osseous lesions following recovery from typhoid fever have been commonly observed. In a large number of cases staphylococci have been obtained from clinical speci-

7. Browder, G., and Meyers, R.: *Am. J. Surg.* 37:4, 1937.

8. Siegling, J. A.: *Illinois M. J.* 72:422, 1937.

9. Moiroud, P.: *Presse méd.* 45:980, 1937.

ing periods, ranging from five to fifteen years. In general, conservative therapy, when successful, brought about healing in an average of fifteen months, the author states. Fistula or abscess developed in 45 per cent of the cases. Of 17 cases of lesions in the long bone treated by surgical extirpation of the focus, in 12 there was healing. The time required for healing in the surgically treated patients averaged seven months. Individual cases are analyzed. In general, if the local tuberculous lesions are in the short bones of the extremities, if they are inaccessible to surgical intervention or if they threaten epiphysal damage to children, they had best be treated conservatively. Conservative therapy is also advised in dubious cases of lesions in the upper extremities, since strains of weight bearing do not exist here. However, operative therapy is advised in the long bones and in the neighborhood of the longer joints, at all ages, as the procedure of choice. Local excision of the focus helps the general resistance in cases in which generalized infection exists.

[ED. NOTE.—Attempts to remove tuberculous foci from the long bones in the past have frequently resulted in deformity and disturbance in growth.]

Kushizaki and Saito<sup>13</sup> report 2 cases of primary muscular tuberculosis, one in a 24 year old man and the other in a 34 year old woman. In the first the lesion was solitary, involving the pectoralis major muscle; in the second case multiple almost symmetrical masses were present in the four extremities. This case presented also calcified hilar nodes. The first patient had no other discernible tuberculous lesions. The masses are difficult to diagnose clinically, since they move with the muscle and are smooth and usually tender. The overlying skin is not involved. Radical excision is advised. Pathologic identification usually is essential to diagnosis, since the masses grossly resemble tumors, parasitic infestation or chronic inflammatory lesions. The more recent literature is carefully analyzed. Colored plates of the operative observations in the 2 cases are reproduced.

#### INVOLVEMENT OF THE BACK

*Surgical Treatment of Pain Low in the Back.*—Ghormley and Wesson<sup>14</sup> present a review of all cases in which patients were subjected to fusion operations at the Mayo Clinic for low spinal and sciatic pain. Operation is advised, after a study to exclude the possibility of neurologic disturbances in patients from 20 to 50 years of age. In this series of 155 cases the average duration of symptoms was five and a half years. The group in which pain of static origin is relieved by rest

13. Kushizaki, S., and Saito, K.: Beitr. z. klin. Chir. **165**:177, 1937.

14. Ghormley, R. K., and Wesson, H. R.: South. M. J. **30**:806, 1937.

symptoms of segmental neuritis which may be attributed to compression of nerves within the intervertebral foramens. Attention is called to two mechanisms by which this compression is brought about, namely, (1) collapse of the walls of the foramens and (2) constriction of the lumens of the foramens. Under the first heading is described thinning of the intervertebral disks (discogenetic disease), arising from various causes, which produces collapse of the anterior half of the foramen, followed by anterior subluxation of the superior articular process of the subjacent vertebra. This condition is often associated with the exostoses typical of hypertrophic spondylitis. Under the second heading is described primary arthritis of the apophysial joints, which may result in ankylosis of the articular facets, the constriction of the foramen being due to periarticular swelling or later to the ossification of synovial membranes. Collapse results mainly from thinning of the disk; hence it begins at the anterior margin of the foramen. Constriction results from inflammation of the synovial membranes of the apophysial joints and therefore begins at the posterior margin. Roentgenograms illustrating the conditions described are presented.

*Injuries to the Accessory Processes of the Vertebrae.*—Mensor<sup>17</sup> stresses the importance of injuries to the spine which involve torsion. Roentgenologic studies of 141 patients who gave a history of such injuries revealed that 22 had fractures involving the accessory processes. Nine of these also had anomalies involving the lamina, pedicle or articular facets. The ratio of frequency of fractures to anomalies was  $2\frac{1}{2}$  to 1. Particular attention is called to the necessity of taking roentgenograms at various angles to show the fractures and anomalies. Excellent reproductions of roentgenograms illustrating the text together with line drawings are included.

*Painful Coccyx.*—In a study of 278 cases of painful coccyx, Duncan<sup>18</sup> observed that in 89 per cent symptoms were preceded by an injury to the coccyx, which usually consisted of a fall in the sitting position. Hence he concludes that coccygodynia is due to a local injury and only rarely is of psychic origin. Ninety-seven per cent of his patients were women. He believes that this large proportion is explained by the more prominent posterior position of the coccyx in women, which makes it more liable to injury. Roentgenologic studies of patients with and without coccygodynia showed that almost any variation except fracture or dislocation was of equal occurrence in the sexes. Conservative treatment, consisting of postural exercises, exercises causing the soft tissues surrounding the coccyx to act as a natural cushion, hot sitz baths, laxatives and local massage is recommended for

17. Mensor, M. C.: J. Bone & Joint Surg. **19**:381, 1937.

18. Duncan, G. A.: Painful Coccyx, Arch. Surg. **34**:1088 (June) 1937.

to the bone in relatively advanced stages. Histologically the tumor is composed of osseous and osteoid tissue. Malignant osteoblasts are separated by relatively large amounts of intercellular osteoid tissue. Spicules of bone and spindle cells representing undifferentiated connective tissue are also found. The tumor apparently arises from pre-osseous connective tissue and rapidly differentiates toward the end product, namely bone. Seventy-two, or about one half, of the tumors occurred in the lower end of the femur or the upper end of the tibia. Four developed in the skull, 10 in the upper or lower jaw, 3 in a vertebra, 4 in a bone on the pelvis and 4 in the scapula. Sclerosing sarcoma occurs most frequently in adolescents and in young adults. There were only 36 patients over 25 years of age. In approximately half of the cases trauma was mentioned in connection with the beginning of the tumor. In some cases there were fever, the patient's temperature being as high as 101 F., and leukocytosis, usually with a white cell count under 18,000. Clinically the swelling was firm, smooth and continuous with the bone. Palpation occasionally revealed crepitus. The diagnosis was made by roentgenologic and microscopic examination.

Roentgenologically the tumor appears to develop in the end of the bone on the side of the epiphysial line toward the shaft. The earliest evidence of the formation of the tumor is sclerosis with obliteration of the normal markings of the bones. The most strongly marked involvement of cancellous bone in the earliest stages is immediately adjacent to the epiphysial line. The earliest indication of periosteal reaction is spicules of bone laid down at right angles to the shaft. Clinically the tumor runs a relatively acute course, the symptoms rarely remaining more than six months. Pain, swelling and impairment of function appear in this order. One hundred and six patients were followed for more than five years or until a fatal termination. Of these, 18, or 17 per cent, were living at the end of the five year period. For all of the latter patients resection or amputation was employed. No five year cures followed irradiation. However, in cases of inoperable tumor in the bones of the pelvis or femur in which pulmonary metastases had occurred, high voltage roentgen therapy seemed to lessen the swelling and decrease the pain for several months. There was no proof that irradiation prolonged life or cured the disease.

*Sarcoma of the Knee Joint Resulting from Roentgenotherapy.*—Sarcoma arising as a result of roentgenotherapy is rare clinically. Fifteen cases have been assembled from the literature. Becker<sup>22</sup> reports such a tumor in a 25 year old woman. At the age of 11, the patient was treated by roentgen irradiation for swelling of the knee, clinically diagnosed as tuberculosis. Tremendous overirradiation was adminis-

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22. Becker, F. D.: *Deutsche Ztschr. f. Chir.* **248**:11, 1937.

the roentgenogram near the internal condyle of the femur, usually cannot be demonstrated until two or three weeks after the injury. Cul-  
len<sup>25</sup> states that the condition should be looked on not as a separate disease but as a local manifestation of post-traumatic changes common to joints. In support of this thesis he calls attention to the fact that the changes, though commonly affecting the tibial collateral ligament, may likewise occur in the tendons of attachment of the adductor magnus or vastus medialis muscle. They have points in common with traumatic myositis ossificans and the opacities of so-called subdeltoid bursitis. Since disagreement has arisen as to whether calcification or ossification is the true pathologic condition under discussion, the author points out that either of the processes may develop about joints after trauma. In the absence of trabeculation, he observes, it is impossible to differentiate the two conditions by the roentgenogram. The theory is advanced that a fatty degeneration may precede the calcific change, accounting for the delay in roentgenographic appearance. The final appearance of calcification or ossification may be related to glandular imbalance prevailing at the time in question.

*Calcification of the Semilunar Cartilage.*—Balensweig and Bosworth,<sup>26</sup> in reporting 2 cases of calcification of the semilunar cartilages of the knee joint, conclude that this lesion has its onset in middle life, may be bilateral, may occur without resulting in either objective or subjective symptoms and apparently is not caused by trauma. They advise operation when the lesion is complicated by cystic formation, or when the cartilage becomes loosened and gives rise to symptoms. Their first patient was a man 66 years of age who complained of pain and swelling on the outer aspect of the right knee. Examination showed a normal status except for arcus senilis of both eyes and the condition in the knee. The knee presented a flexion deformity of 30 degrees and localized swelling and tenderness over the external cartilage. Roentgenograms showed calcification of the external cartilage of both knee joints. Meniscectomy was done and the patient made a good symptomatic recovery. The second patient was a woman 44 years of age who complained of acute pain in the right knee. Examination showed a 5 degree flexion deformity and thickening and tenderness of the soft tissues of the joint. Roentgenograms revealed calcified menisci. At operation both cartilages were seen to contain calcium and were removed. The patient made a good symptomatic recovery. The proportions of uric acid and sugar in the blood were determined in the first case and were reported normal.

[ED. NOTE.—In the opinion of one of us this condition is not uncommon.]

25. Callen, H. S.: *Radiology* 29:158, 1937.

26. Balensweig, I., and Bosworth, D. M.: *Surgery* 2:120, 1937.

teaching that normally 20 degree plantar-dorsal flexion is present in Chopart's joint, Zimmerman,<sup>30</sup> who tested some children and adults by attempted plantar immobilization of the hindpart of the foot, reports that children show 10 to 15 degrees of such motion and adults 5 degrees. The increased ranges in feet with ankylosis at the ankle joint was a compensatory development.

*Gas Gangrene Treated With Sulfanilamide.*—Bohlman<sup>31</sup> reported 3 cases of gas gangrene treated with sulfanilamide. The patients had prophylactic doses of a combined gas bacillus antitoxin. All responded promptly to sulfanilamide. Pending further study the author's conclusions were: 1. Conservative surgical principles should be combined with the use of the drug. 2. Sulfanilamide probably had a specific effect on gas bacilli, but the results may have been due to its checking symbiotic growth of streptococci.

#### ORTHOPEDIC OPERATIONS

*Shelving Operation for Dislocated Hips.*—Smith<sup>32</sup> carefully analyzes 67 cases of congenital dislocation of the hip. He concludes that patients with untreated unilateral dislocations have a good chance of reaching the age of 15 without symptoms, but that it is unlikely that they will reach the age of 40 without being forced to seek medical aid. Patients with bilateral dislocation of the hips complain of pain or fatigue before the age of 10 and cannot be expected to reach 20 without disability. The shelving operation has proved successful in ameliorating symptoms, especially if performed after the age of 10 and if the condition was unilateral. In younger patients the results were poor.

*Femoral Bifurcation With the Aid of the Trochanter Minor.*—In cases of irreducible old congenital dislocation of the hip in which the lesser trochanter is opposite the region of the original acetabulum, Hass<sup>33</sup> performs a transverse osteotomy below the lesser trochanter in order to get this trochanter to rest against the acetabulum. This is possible in all cases of forward, lateral or intermediate dislocation. It is a modification of the osteotomy which has given the author a stable painless hip. He differentiates it from the level advised by Lance as being aimed at getting the lesser trochanter into the acetabulum, whereas Lance tries to implant the femur itself below the lesser trochanter into the original socket.

30. Zimmerman, M.: Ztschr. f. Orthop. **66**:21, 1937.

31. Bohlman, H. R.: Gas Gangrene Treated with Sulfanilamide: Report of Three Cases, J. A. M. A. **109**:254 (July 24) 1937.

32. Smith, A. R.: Ann. Surg. **106**:92, 1937.

33. Hass, J.: Ztschr. f. Orthop. **66**:353, 1937.

scapular muscles was carried out in 2 cases, 1 of which is old enough for a report. After three years practically normal use of the arm and shoulder has been restored with no increase in lateral deformity of the upper thoracic part of the spine. Line drawings and photographs are given.

#### FRACTURES

*Faultily United Colles Fracture.*—Campbell<sup>37</sup> reports a new operation to correct the deformities due to malunion of Colles fractures. Shortening of the radius, angulation of the radial articular surface and prominence of the styloid process of the ulna are all corrected, whereas procedures such as radial osteotomy or resection of the lower end of the ulna correct only one or two of the deforming elements. The operation consists of osteotomy of the radius with insertion at the site of osteotomy of a pyramidal wedge of bone taken from the lower end of the ulna. This procedure has been carried out in 19 cases; 11 of the 12 known end results were excellent.

*Dislocation of the Semilunar Bone.*—In general, dislocations of the semilunar bones should be reduced if at all possible. Open reduction is possible three, four or even six weeks after displacement. Nell<sup>38</sup> reports that Böhler, using mechanical distraction at open operation in one case, reduced a six month old dislocation. As a rule the end results are good in these reduced dislocations of the semilunar bones. Fractures of the semilunar bones rarely form pseudoarthroses and operative excision is indicated only rarely, in cases of comminuted fractures. Long fixation may be required. Extirpation is reserved for malacia of the semilunar bones which has been treated for at least six months by efficient rest without success. If arthritis deformans is visible on the roentgenogram, it is too late to operate, since the function will not be improved or the pain lessened. To spare the remaining important ligaments of the wrist the author advocates the palmar incision. The dorsal incision, while easier to perform, injures many ligaments and later results in serious carpal disturbances. It is difficult to avoid traumatizing the adjacent cartilages of the joint through this incision, since extensive stripping is required. A curved tenotome helps to free the bone at operation, dividing only the ligaments which are attached to the semilunar bone. A 5 to 6 cm. longitudinal incision is used, commencing 1 cm. above the pisiform bone. The median nerve and the flexor muscles of the fingers are retracted toward the ulna.

*Fractures of the Terminal Phalanxes.*—Perschl<sup>39</sup> discusses small fractures of the tip of the terminal phalanxes. These are often caused

37. Campbell, W. C.: Malunited Colles' Fractures, J. A. M. A. **109**:1105 (Oct. 2) 1937.

38. Nell, W.: Beitr. z. klin. Chir. **165**:619, 1937.

39. Perschl, A.: München. med. Wchnschr. **84**:810, 1937.

*Experimental Sprains in the Joints.*—Miltner and his co-workers<sup>42</sup> in the study of sprains in the joints were able to produce manually mild and severe forms of sprain in the knee joints of rabbits. After the trauma the joints were examined roentgenologically to exclude the possibility of fracture and subsequently representative animals were killed at weekly intervals and the gross and microscopic effects of the injury studied. These experiments showed that trauma applied to joints causes an acute inflammatory reaction at the points of greatest injury. In severe injury the bony or cartilaginous structures may be involved. In 12 rabbits mild sprains were produced, and necropsies were performed weekly to the sixth week. The trauma caused an acute inflammatory reaction with exudation of synovial fluid, edema of the subsynovial and periarticular connective tissues and moderate fibroblastic proliferation and leukocytic infiltration. Gross evidence and external signs of pathologic change disappeared by the fourth week, but microscopic evidence of inflammation, slight edema and fibrosis persisted until the sixth week. Hence it was suggested that the joint should be protected for at least two weeks after the clinical signs have disappeared.

On the 11 rabbits with severe sprains autopsies were done from one to eleven weeks later. There was inflammatory reaction of the soft tissues similar to the changes seen in the first group but more severe. These changes in the soft tissue persisted to the eighth week and gradually resolved during the next two weeks. In addition to the changes noted in the first group, detached bits of bone too small to cast shadows in roentgenograms were usually seen at the ligamentous-osseous junction. A degeneration of the cells also was observed in the intermediate zone of hyaline cartilage of the tibia on the side of the joint opposite to the sprained ligaments. In one case a traumatic fissure in this intermediate zone of cartilage was noted. It is thought that in this slow degeneration of cartilage may lie one of the causes for chronic traumatic arthritis.

*Pathologic Study of Tendons.*—Günther,<sup>43</sup> in a study of pathologic material from fascia, tendons and ligaments, concludes that tendons and ligaments may be affected by diseases and inflammatory conditions much as is a bursa. He shows the progressive nature of changes in ligamentous structures: inflammation of the ligamentous structures, changes in the proliferation of the fibers of connective tissue and hyaline degeneration. He traces the development of Dupuytren's contracture and the formation of tumors from simpler pathologic alterations.

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42. Miltner, L. J.; Hu, C. H., and Fang, H. C.: Experimental Joint Sprain: Pathologic Study, *Arch. Surg.* 35:234 (Aug.) 1937.

43. Günther, G. E.: *Beitr. z. klin. Chir.* 166:32, 1937.



proved cases of mesenteric lymphadenitis. Quenu <sup>45</sup> and Marchant <sup>46</sup> conciliated these observations by stating that there was an alteration in the appendixes in some of these patients but not in others.

The appendixes of nineteen of the patients in the present series were examined microscopically, and only eight showed any evidence of pathologic change. In one appendix there was hypertrophy of the lymphoid follicles; four showed acute inflammation and one subacute inflammation; one contained *Oxyuris vermicularis* and showed focal infiltration with polymorphonuclear leukocytes and eosinophils, and in one there was focal ulceration confined to the submucosa.

Royster <sup>42</sup> thought that the cause in some of these cases of mesenteric lymphadenitis was a lymphatic block around the appendix and that the removal of the appendix mechanically released the block. Freeman <sup>4</sup> pointed out that involvement of the lymph gland in mesenteric lymphadenitis is usually quite diffuse throughout the abdomen and that the lymphatic drainage of the appendix is local. It should be emphasized that the appendix is a part of the large bowel and that it is a well known fact that the mesenteric lymph glands are frequently not enlarged in cases of acute or of chronic appendicitis.

It may be possible that a kinking, twisting or obliteration of the lumen of the appendix may be a factor in some patients. However, an anatomic condition of this character was found in the appendix in only two patients in the present series and consisted of a kinking of the organ.

Brown, <sup>40</sup> Royster <sup>42</sup> and others, who believed that the appendix was the essential causative factor in mesenteric lymphadenitis, advocated appendectomy. Royster <sup>42</sup> reported that following this treatment none of his patients had any further trouble.

Apparently, however, appendectomy does not cure all of these patients, for Marshall <sup>19</sup> followed up an unstated number of his twenty-six patients after appendectomy and found that four of them had attacks postoperatively. This observation is further confirmed by Schnitzler's <sup>47</sup> experience. Appendectomy was performed on his patient, and eight years later the patient was operated on by him under the mistaken idea that appendectomy had not been performed previously. Simple mesenteric lymphadenitis was found at this second laparotomy, and, furthermore, the patient subsequently continued to have similar attacks.

Similarly, in the present series, a boy aged 7 years, who presented the clinical picture of acute appendicitis, underwent an appendectomy on May 1, 1933. He was free from symptoms the following two months.

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45. Quenu, cited by Bertein and Worms.<sup>1</sup>

46. Marchant, G.: Adénite dans l'appendicite, Bull. et mém. Soc. de chir. de Paris 26:77-81, 1900.

47. Schnitzler, H.: Lymphangitis et Lymphadenitis mesenterialis, Wien. klin. Wchnschr. 46:134-137 (Feb. 3) 1933.

another attack of mesenteric lymphadenitis since operation, but four were found to have attacks much like those present before operation.

It would seem, however, that the weight of evidence is against those who believe that an infection from the appendix can be excluded as a causative factor in mesenteric lymphadenitis. The percentage of recoveries after appendectomy seems too high to be a mere coincidence. Since most of the patients are free from symptoms after removal of the appendix, appendectomy is apparently indicated when simple mesenteric lymphadenitis is present and no cause other than the appendix is found for its presence. It may be, as suggested by Schnitzler,<sup>47</sup> that an infection in the appendix and one in the mesenteric lymph glands do not occur *pari passu* and that the lesion of the appendix has healed by the time the glands become enlarged.

In regard to another portal of infection, Brennemann<sup>5</sup> suggested that bacteria may be transmitted from the throat by the blood stream or may be swallowed and produce localized inflammatory lesions in the intestines with secondary involvement of the lymph glands. Cultures of material from the throat by Goldberg and Nathanson<sup>20</sup> invariably showed *Str. haemolyticus* and in addition some showed *Staphylococcus haemolyticus*. They thought the mode of infection to be hematogenous. In the present series of twenty-two patients, there were fifteen (68 per cent) who presented evidence of infection of the upper respiratory tract at the time of operation or just preceding it. It is reasonable to suppose that a higher percentage would have been found if such evidence had been carefully looked for in every instance. The incidence here recorded is based on the routine hospital records, and it is quite probable that a critical evaluation as to the presence of an infection of the throat at the time of or immediately preceding operation, not always a simple matter at best, was not made in all cases. Coleman<sup>10</sup> stated that in his patients the infection seemed to come from the respiratory or the intestinal tract. Ninety per cent of his patients had enlarged cervical glands.

Guleke,<sup>37</sup> in common with most observers, expressed the belief that the etiologic agent came from the bowel. Various factors which might favor the passage of bacteria or their toxins through the wall of the bowel have been suggested. Distention, catarrhal inflammation, abrasions of the mucous membrane and lowered resistance of the surface epithelium of the bowel were thought to be important in the production of mesenteric lymphadenitis according to Bell,<sup>33</sup> Pribam,<sup>41</sup> Freeman<sup>4</sup> and Signorelli and Hosen.<sup>9</sup>

Marshall<sup>19</sup> resected a portion of the cecum with the appendix of one patient and found no catarrh of the cecum microscopically. Stained sections were made of the wall of the bowel for bacteria in the fatal case of the series which forms the basis of this report. but no organisms were found.

## CONCLUSION

The opinion regarding the etiology of mesenteric lymphadenitis are numerous and varied. There is one group of investigators who believe that it is due to tuberculosis, but there is also a large group who found no evidence of tuberculosis by test or by culture. It seems that there is no definite evidence either in the literature or from tests made on the patients in the present series that the virus of lymphogranuloma venereum or *B. melitensis* plays any part in the production of this condition. It is concluded that the infection in some patients does and in some does not appear to originate from the appendix. Many observers believe that these infections come from pyogenic infection in the throat which enters the glands by the blood or through the wall of the bowel. It would appear from the observations reported and from a careful review of the literature that not one but several factors are capable of producing mesenteric lymphadenitis.

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NOTE.—Since we made this report there have been added two interesting cases of mesenteric lymphadenitis. In one a ruptured mesenteric gland was found at autopsy, and in another, regional ileitis.

powers of further differentiation which were inherent in the original cells at the time of their separation.

The epidermoid tumor is an embryonal neoplasm composed of tissues derived entirely from ectodermal elements. Certain of the cranio-pharyngiomas, e. g., the cholesteatoma and the simple adamantinoma, properly may be considered to fall within this classification. Although the epidermoid tumor is the most frequent form of intracranial embryonal tumor, it is interesting that not a single epidermoid tumor has been reported as arising from the pineal body. The significance of this observation will be discussed later.

The teratoid tumor is an embryonal growth composed of tissues derived from both ectodermal and mesodermal elements. Certain of the more complex craniopharyngiomas might be considered to fall within this classification. The common clinical "dermoid" tumor, usually made up of a fibrous sac bearing hair and sebaceous material, is in reality a teratoid tumor of limited character. It is our opinion that the four cases reported in the literature as dermoid tumors of the pineal body should be classified as teratoid tumors and we are so referring to them hereafter in this paper.

The teratoma is an embryonal tumor composed of tissues derived from all three primitive layers. A tumor of this type is comparatively infrequent within the cranium. Teratoma of the pineal gland has been reported and the diagnosis proved in only thirteen instances prior to the case reported here.

A chorionepithelioma is an embryonal neoplasm in that it is composed of primitive cells derived directly from the fetal epiblast. The usual source of a chorionepithelioma is the fetal epiblast of the retained placenta; nevertheless, such a tumor is occasionally encountered as a spontaneous evolution from the germinal epithelium of the ovary or the testis. One instance of chorionepithelioma primary in the pineal body has been reported by Askanazy. This tumor must be considered as an embryonal neoplasm that had taken origin from a primitive cell group comparable to the germinal epithelium of the testis and that had differentiated up to the level of the fetal epiblast. However, as the tumor presents no evolved ectodermal or mesenchymal tissues, it cannot be classified as an epidermoid or teratoid tumor or as a teratoma and is therefore given an individual subgrouping with the embryonal neoplasms.

#### MIXED TUMORS

In addition to the true embryonal neoplasms listed, mention should be made of the "mixed" or "compound tumor" of the pineal body, which is made up of two or more differentiated neoplastic elements. Reports

TABLE 1.—Data on Embryonal Tumors of the Pineal Body Reported in the Literature

Case No.	Date	Author	Sex	Age, Yr.	Clinical Data	Duration of Illness	Location, Type and Size	Pathologic Picture			Comment
								Ectoderm	Mesoderm	Endoderm	
TERATOMAS *											
1	1875	Welgert	M	14	Patient admitted in comatose state; emaciated	.....	3d ventricle; cystic; 1½×1½ inches	Squamous epithelium, cornified; hair; hair follicles; sebaceous glands; nests of pineal tissue; nonmedullated nerve fibers	Connective tissue; fat; cartilage; smooth muscle	Columnar epithelium with papillary formation	
2	1889	Gauderer	M	12	Frontal headaches; patient lethargic in thought and action; well nourished; late signs of local and general compression	.....	3d ventricle; cystic; 3.5×2.5 cm.	Squamous epithelium; hair; sebaceous glands	Connective tissue; hyaline cartilage; fat; bone; osteoid tissue; smooth muscle	Columnar epithelium, mucosal type	
3	1890	Gutzelt	M	8	Frontal headaches; genital precocity; lethargy; late signs of local and general compression	8 mo.	3d ventricle; cystic; 4×3.25 cm.	Epidermoid epithelium; hair; sebaceous glands	Connective tissue; cartilage; fat; smooth muscle	Columnar epithelium	
4	1900	Neumann	M	27	Midfrontal headaches; lethargy; signs of local and general compression	7 wk.	3d ventricle; cystic; 4×3×2.5 cm.	Squamous epithelium, cornified; cholesterol-filled cysts; epidermoid carcinoma; pineal tissue	Connective tissue—sarcoma (?); hyaline cartilage; fat; lymphoid tissue; blood vessels—hemangioma; smooth and striped muscle	Columnar epithelium with cuticle and gland formations	
5	1909	Frankl-Hoehwart	M	5½	Overgrowth; macrogenitalia; adiposity; hypertriehosis; maturity of voice and mental status; late signs of local and general compression; congenital defects—bronchial fissure, nevi and hemangiomas	2½ yr.	3d ventricle; cystic; 5×2.5×2.9 cm.	Squamous epithelium, cornified; pineal tissue	Connective tissue—sarcoma (?); hyaline embryonal cartilage; osteoid tissue; round cell infiltration	Columnar epithelium with goblet cells and gland formation	Congenital familial defects; tumor of the pineal body diagnosed before death on basis of macrogenitosomia praecox
6	1913	Hijmans, van den Bergh and van Hasselt	M	8	Overgrowth; macrogenitalia; hypertriehosis; maturity of voice and mental status; polyuria; polydipsia	.....	3d ventricle; cystic	Squamous epithelium, cornified; hair; sebaceous glands; pineal tissue; ganglion cells; nerve fibers; epithelioid cells of indeterminate character in nests and syncytial masses	Connective tissue; bone; cartilage; lymphoid tissue	Columnar epithelium	Epithelioid nests suggest chorionepitheliomatous structure; teratoma of the pineal body diagnosed before death on basis of macrogenitosomia praecox
7	1913	Huetter	M	19	Headache; signs of general compression	.....	3d ventricle; size of pigeon's egg; lum; pineal tissue	Squamous epithelium; pineal tissue	Connective tissue; smooth muscle	Columnar epithelium with gland formation of the gastrointestinal type	No histopathologic report with original presentation, but complete picture is presented in illustrations by Terhune

Case No.	Date	Author	Sex	Age, Yr.	Clinical Data	Duration of Illness	Location, Type and Size	Pathologic Picture			Comment
								Ectoderm	Mesoderm	Endoderm	
14	1934	Bochner and Searff	M	9½	Severe peridole frontal headaches; lethargy and vomiting with headaches; late signs of general compression Toothlike structures in roentgenograms	2 yr.	3d ventricle; cystic; 5.5×3.5×5.5 cm.	Teeth—adamantinomatous embryonal anlage and adult teeth, including dentine, dental pulp and enamel; hyperplastic pinal tissue; nerve tissue and glial structures	Connective tissue, embryonal and adult; hyaline cartilage; fat; membranous and lamellar bone with the Haversian canals	Columnar epithelium with cilia and goblet cell formations; simple and compound racemose glands and thyroid tissue	Tumor diagnosed as embryonal tumor (clinically) on basis of toothlike structures in roentgenogram; no metabolic disturbances. Tissues of note: (1) teeth, all forms from primitive to adult; (2) hyperplasia of pinal elements; (3) complete formations of mucosa of upper respiratory tract; (4) thyroid gland
TERATOID TUMORS											
15	1911	Bailey and Jelliffe	M	12	Overgrowth; obesity; pallor; infantile status of voice and genital; signs of local and general compression; patient mentally sluggish; calcified bodies in roentgenogram	10 yr.	Over quadrigeminal plate and in 3d ventricle; 1½ inch	Sebaceous material; hair	Cartilage	.....	"Dermoid" tumor
16	1921	Glebel	M	15	None given						
17	1925	Horrax and Bailey	M	3	Overgrowth; macrogenitalia; hypertrichosis; drowsiness; headache; signs of local and general compression	3 yr.	Over quadrigeminal plate and in 3d ventricle; cystic; 7×4 cm.	Squamous epithelium, cornified; hair; hair follicles; sebaceous and sweat glands	Connective tissue	.....	
18	1930	Altmann	M	11	Overgrowth; macrogenitalia; hypertrichosis; headache; drowsiness; signs of local and general compression	Few mo.	3d ventricle; cystic; 4.5×4×5.5 cm.	Squamous epithelium, cornified; hair; sebaceous glands	Cartilage; bone; fat	.....	
19	1903	Askunazy	M	19	Severe headache; signs of general compression	2 wk.	Over quadrigeminal plate; solid; size of a walnut	Squamous epithelium, cornified; hair; sebaceous glands	Connective tissue; cartilage; fat; lamellated bone	.....	Adult type of testes; early spermatogenesis
NONDIFFERENTIATED TUMOR											
19	1903	Askunazy	M	19	Severe headache; signs of general compression	2 wk.	Over quadrigeminal plate; solid; size of a walnut	Pinal tissue; syncytial masses and single large cells with frequent mitoses	Vascular tissue, abundant	.....	Chorionepithelioma

their cells possessed only that potentiality for further differentiation which was left in the already partially evolved epithelium from which they had taken origin.

Embryonal tumors which arise from the pineal gland present a decided contrast to the foregoing types of tumors, for there is much evidence to suggest that these tumors take their impetus to grow from a fundamental multipotentiality inherent in the primitive pineal cells.

The very complexity of an embryonal tumor of the pineal body, such as the one we shall describe, calls for the departure of the germinal cell groups very early in the life of the embryo, that is, close to the blastomere stage, whereas the pineal body does not appear as an entity until a much later date, that is, after the closure of both the dorsal and the ventral invagination. It is obviously difficult, if not impossible, therefore, to account for the location of cells in the pineal body which might have sufficient multipotentiality to produce such a complex tumor by any process of tissue inclusion or transplantation from the already partially formed integument.

Multipotentiality in an adult tissue is generally attributed only to cells found in the testis and the ovary. Numerous points of similarity, however, do exist between the pineal body and the testis, in both cell structure and neoplastic formation. The marked resemblance of the cell type of the pineal adenoma (pinealoma) to that of the spheroidal cell tumor of the testis (seminoma) has been stressed by Harris and Cairns. Van den Bergh and also Boehm have reported finding in pineal teratomas "epithelioid cells of an indifferent character" having the essential characteristics of the interstitial cells of the testis. Actual chorionepithelial elements in tumors of the pineal body have also been described by Askanazy and by van den Bergh. The pineal body ranks second to the testis as a source of multipotential neoplastic material, and together they form the principal locations of teratomas in the male.

Finally, the multipotentiality of the primitive pineal cells is further attested by the comparative embryology and anatomy of that body. It has formed an eye in the cyclostomes, racemose glands in some birds and the structure of an endocrine gland in the mammal.<sup>2</sup>

#### CLINICAL MANIFESTATIONS OF PINEAL TUMORS

The clinical manifestations of tumors of the pineal body fall into two groups, the mechanical and the constitutional (or endocrine).

Mechanical obstruction of the ventricular system gives rise to the classic symptoms and signs of increased intracranial pressure. A peculiarity of diagnostic value, at times encountered in tumors of the

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2. This thesis has been presented repeatedly by Tilney; see his text and the discussion following the paper on "Pinealomas" by Globus and Silbert.

mental evidence as to the endocrine function of the pineal body has been irregular but of sufficient interest to be noted here. Foa removed the pineal bodies in chicks from 11 to 93 days of age. He found an increased rate of development from two to five months after the operation, and at from eight to fifteen months (at autopsy) there was demonstrated a decided overgrowth of both testes and combs. Horrax pineal-ectomized guinea-pigs and also found an overgrowth of the testes at autopsy. On the other hand, Dandy, working on dogs, and Anderson and Wolf, using rats in a carefully conducted series, found that the operation had no influence on sexual development (Dandy) or on the rate of growth, age of puberty or weight of other endocrine organs (Anderson and Wolf). Rowntree and his co-workers injected pineal extract (Hanson) into the peritoneal cavities of rats daily for five generations. They noted a decided retardation of the rate of growth and an acceleration of the rate of development and maturation.

Askanazy considered the phenomenon of macrogenitosomia praecox as a "pseudo-pregnancy state" induced by the presence within the body of an embryonal tumor. He cited the case of Sachi, in a boy of 9 years, in whom since the age of 5 skeletal overgrowth and changes in the voice had developed. The testicular tumor, which proved to be a teratoma, was removed, and shortly thereafter the boy returned to a normal preadolescent state. Experimental support of this thesis is offered by Starling, who injected the products of macerated rabbit embryo into immature female rabbits and produced precocious sexual overgrowth and maturity. The more recent development of the Aschheim-Zondek phenomenon as a test for pregnancy, or rather for the overflow of hormones associated with pregnancy, has led to the startling finding that the urine of a person bearing an embryonal tumor will induce (apparently in the same manner) precocious maturity in immature female rabbits.<sup>5</sup> These findings are entirely in keeping with the observed greater incidence of precocity in cases of true embryonal tumor of the pineal body, but obviously do not entirely answer the problem.

Our patient, although bearing a highly complex teratoma of the pineal body, failed to show any of the characteristic features of macrogenitosomia praecox. The difficulty in attempting to establish an exact relationship between a pathologic process of the pineal body and sexual

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5. Zondek found that the urine of a person with a malignant growth, and more particularly a malignant growth of the genitals, frequently gave a positive reaction for a follicle-stimulating hormone—in 81.8 per cent of cases of malignant growths of the genitals and in 20.4 per cent of cases of extragenital malignant growths. Ferguson studied 117 cases of teratoma of the testes and established the importance of the quantitative test for a follicle-stimulating hormone in the differential diagnosis of tumors of the testes.



the grounds of a probable tumor of the third ventricle, but this action was postponed by the family because of temporary symptomatic improvement.

Occasional attacks during the period between September and the following May, although severe, did not greatly interfere with the patient's daily routine. He was able to continue at active work and play until May 7, 1933. On that morning he complained of headache and sleepiness more marked than usual. Two hours later his mother found him still apparently asleep but very pale. She had great difficulty in arousing him. That evening, because of the persistence of this semistuporous state, he was taken to the hospital.



Fig. 1.—The patient (with bat) at play with his brothers, two weeks prior to his death at the age of  $9\frac{1}{4}$  years.

*Physical Examination.*—The boy was found to be well developed, drowsy and apathetic. The fundi showed early bilateral papilledema. The deep reflexes were diminished, and Babinski and Chaddock signs were present bilaterally. Examination, as far as it could be carried out at that time, otherwise gave negative results.

The following morning he seemed somewhat better. Roentgenograms of the skull showed evidence of increased intracranial pressure as well as the calcified bodies in the area of the interbrain. It was noted that these calcified bodies bore a remarkable resemblance to the nonerupted teeth to be seen in the mandible. A clinical diagnosis of embryonal tumor of the area of the interbrain, probably

dilatation of the pupils and marked irregularity of the pulse. There were cyanosis and an irregular Cheyne-Stokes type of respiration. Fifty cubic centimeters of a 50 per cent solution of dextrose was given intravenously, after which the pulse and respirations became essentially normal, and the child's appearance was much improved. Immediate trephine and ventricular tap were decided on in order to combat the acute phase of intracranial pressure. The child, seemingly in fairly good condition, was being gently lifted from the bed to the stretcher when respiration ceased. All attempts at resuscitation failed.

*Necropsy.*—Gross Examination: The body was that of a well developed rather well nourished boy. The skin was smooth and soft, bearing no pubic or axillary hairs. The head was covered with a normal growth of light brown hair. The external genitalia appeared normal in all respects. The testicles were descended.

The examination was limited by the family to the head. The scalp stripped readily. The calvarium raised with little difficulty, though the dura was moderately adherent thereto. The brain was removed, revealing a not remarkable cranial base. The venous sinuses contained soft postmortem thrombi. The ethmoid and sphenoid sinuses were free from purulent material. The middle ears were not remarkable. The brain was symmetrical and well formed and weighed 1,535 Gm. The pia-arachnoid was markedly engorged. The basilar vessels were normal in structure and arrangement. The gyri were decidedly flattened and the sulci narrowed. Bulging of the floor of the third ventricle was apparent, raising and flattening the optic tracts. The hypophysis was not involved.

Coronal and midsagittal sections, made through the area of the interbrain, revealed a large cystic tumor filling and greatly distending the third ventricle. The foramina of Monro, though enlarged, were occluded by the position of the tumor mass, with resultant hydrocephalic distention of the lateral ventricles. The tumor mass measured 5.5 by 5.5 by 3.5 cm. in its greatest diameters. It extended forward to displace the anterior commissure and backward to overlies and compress the quadrigeminal plate. The corpus callosum and splenium were raised and attenuated. The thalami were displaced and compressed to caplike structures. The body of the tumor lay free in the cavity of the third ventricle but for its anchorage at the region of the tela and the pineal body. The recess of the pineal body was identified, but no vestige of the pineal body was recognized. The aqueduct of Sylvius was patent, though the quadrigeminal plate was much flattened.

The tumor was made up of two principal portions, the posterior and larger portion being a firm, grossly nodular cystic mass, and the anterior portion, a large single thin walled cyst. The cyst was smoothly lined and filled by a milky limpid fluid. The structure of the mass was of a firm fibrous tissue, riddled by intercommunicating cysts and channels. These spaces contained a milky fluid similar to that of the large anterior cyst and were similarly smoothly lined. Just to the left of the midline there was a series of bony hard bodies loosely fixed in shell-like capsules. They had the general appearance of well formed teeth. The largest of these measured 7.5 mm. in diameter and presented two well formed cusps. The lower portion of the tumor was largely made up of an irregular soft structure. An extension of this softer material formed a horizontal mound over the entire rear portion of the tumor, lying on and compressing the quadrigeminal plate. On this mound and extending over its entire length, there was a collapsed saclike structure, which when distended measured 1.5 cm. in diameter. The sac was blind on the left, and on the right it was continuous with the chain of cystic spaces of the denser portions of the tumor.

Microscopic Examination: Frozen and paraffin sections were prepared and stained by hematoxylin and eosin, Van Gieson stain for connective tissue, sudan III

for fat, Hortega's silver carbonate for neuroglia and Bielschowsky and Plien's stain for nerve cells.

Connective tissue stroma of varying density formed the larger portion of the tumor mass. In some areas it was fibroblastic, in others the tissue was more mature, even forming dense collagenous and hyalinized bands. Areolar tissue was widely spread throughout the mass and similarly presented both young and mature cell formations.

The tooth structures noted in the gross specimen showed all stages of dental evolution, ranging from the primitive ameloblastic ridge to completely formed multicuspid teeth. Irregular dental bud elements formed arrangements typical of the adamantinomas of the craniopharyngioma or suprasellar cyst group. There was the typical central mass of loosely scattered small stellate cells, bordered by a ribbon of flattened intermediate cells and the tall clear palisade of ameloblasts. In areas the structure took on the more regular arrangement of the dental bud, forming a hood to the richly vascular dental pulp. The pulp was formed of rather large compactly arranged stellate cells having the general appearance of fibroblasts. The invaginated portion of the layer of ameloblasts was of larger cells and formed the inner enamel epithelium. The outer ribbon of ameloblasts was atrophied and formed the flattened cells of the outer enamel epithelium. At one point the outer enamel epithelium became thickened, forming a mound of large cuboidal primitive ameloblasts—the secondary dental germ structure. The layer of odontoblasts had similarly been differentiated from the dental pulp along its line of contact with the inner enamel epithelium. The odontoblasts formed the typical palisade of tall columnar cells, having well defined cuticular margins and the usual basilar irregularity. The more matured dental structures had a layer of dentine deposited over the row of odontoblasts as a homogeneous pink-staining and finely lamellated structure. Well formed homogeneous enamel substance surmounted the dentine. The ameloblastic organ of the mature tooth appeared as atrophic strands, whereas the dental pulp, on the other hand, had become more prominent and more vascular, forming the permanent dental pulp body. No root structures had developed, although a number of bony spicules were present at the bases of the fibrous dental capsules. Six completely formed teeth were recognized. There were many others, more irregular, both complete and fragmentary, to be seen in a series of sections. Stained with hematoxylin and eosin, the dentine appeared red and the enamel blue; with Van Gieson stain, the dentine was a deep red and the enamel a yellowish brown.

Osteoid tissue and a number of foci of primitive membranous bone formations were frequent. The bony spicules were richly bordered by deeply staining polygonal osteoblasts as well as occasional large mononucleated and multinucleated osteoclasts. More compact masses of mature lamellar bone were present, in large part showing complete haversian systems and readily identified periosteum. Masses of noncalcified richly cellular hyaline cartilage were bordered by well defined perichondrium.

Epithelium, characteristic of the gastro-intestinal and respiratory tracts, formed the lining of the many cysts and spaces. This was for the most part made up of a tall palisade of ciliated cells having well defined cuticular borders. Goblet cells were numerous and were for the most part distended by a clear foamy material, apparently mucinous. In some areas the cells were flattened and irregular; nevertheless the fundamental cell type was similar throughout. Underlying the epithelial layer there was a condensation of fibrous stroma, which in areas had the appearance of hyalinized smooth muscle. Van Gieson's stain, however, indicated the mesenchymal character of the structures.



Fig. 7.—High power photomicrographs of sections showing bone and cartilage formation. *A* shows lamellar bone; note the Haversian system and the periosteum. *B* shows membranous bone; note the osteoblastic activity. *C* shows hyaline cartilage; note the perichondrium and fibro-areolar tissue.

There was much glandular tissue, in places showing direct origin from infoldings of the epithelium lining the cystic spaces. These varied from the simple tubular to the compound racemose architecture of the mixed seromucinous type. The latter structures closely resembled submaxillary salivary glands, being made up of mucinous acini and serous "parietal" or "demilune" collections of cells. The tissue, on the whole, closely simulated the active mucosa of the upper respiratory tract, particularly that of the nasopharynx.

Thyroid tissue formed two isolated islands of acinous structure. The epithelium lining the well rounded acini was of the typical cuboidal type, possessing large well rounded nuclei. Many of the acini were filled with homogeneous pink-staining colloid, characteristically retracted.

Nerve tissue elements were widely scattered throughout the tumor. The more abundant collections formed the softer areas noted at the gross examination at the lower portion of the tumor. The glial cells were largely astrocytes, although glioblasts were not infrequent. A number of giant astrocytes were made out, some multinucleated. Nerve cell bodies were abundant, both as the rounded ganglionic form and as the large pyramidal form. The cytoplasm was ample and for the most part rather granular. The nuclei were well defined and rounded and contained sharply outlined and deeply stained nucleoli. Straight nerve fibers were seen to leave the cell bodies and in places to run for some distance in the plane of section. The numerous small islands and strings of neural elements, scattered through the fibrous stroma of the mass, were placed in sharp contrast by the Van Gieson stain.

Pineal structure, in its characteristic mosaic of large and small cells, was found as scattered groups throughout the hindportion of the tumor mass. Occasional small laminated calcareous nodules, psammoma bodies, were found in these areas. There was, however, no further evidence of involutionary change, as might be expected at the age of 9 years; rather the richly cellular character and the distinct mosaic formation were typical of the pineal gland as seen in infancy and in early childhood. Further forward in the tumor and closely associated with the widely scattered neural elements, there were numerous irregular groups of round cells. These cell groups, though not presenting the same mosaic formation, were strongly suggestive of the pineal element. They were largely made up of the smaller cell type, although there were some scattered larger cells, singly and in small groups, an arrangement found in the midfetal pineal body.

#### ANALYSIS OF THE CASE REPORT

The diagnosis of teratoma was established primarily by the embryonal nature of the neoplasm and secondarily by its tridermal character. The structure of the tumor was such that it must necessarily have arisen from a primitive cell group which had been isolated during early embryonal life and had later differentiated in the direction of its retained potentiality. The tridermal character of the neoplasm was richly manifest in both embryonal and adult tissue structures. Ectoderm contributed nerve cell and axonal structures, neuroglia and pineal and dental elements. Mesoderm formed the connective tissue stroma, cartilage, areolar tissue and osteoid, membranous and lamellar bone. Endoderm formed the ciliated columnar epithelium and glandular structures of the upper respiratory tract and the thyroid gland.

The pineal origin of the neoplasm was evidenced on gross examination by its anchorage at the site of the pineal body and complete replacement of that body and on microscopic examination by the finding of pineal tissue, of the type generally found in infancy, as an integral part of the tumor mass.

Teeth, in all stages of their development, formed the unique feature of this case and are here reported for the first time in a teratoma of the pineal body. The progressive serial relationship of the primitive dental buds to the mature well formed teeth gives the complete picture of dental evolution. In the available literature, considering all types of intracranial neoplasms, there is but one other case in which adult tooth structures are described, and that is a case of teratoma of the pituitary body reported by Hugo Beck.<sup>6</sup> Boehm reported a case of teratoma of the pineal body in which he found elements of the primitive enamel organ, but there were no evolved tooth structures. Ameloblastic cell groups without further dental formations are frequently present in craniopharyngiomas (suprasellar cyst, adamantinoma and ameloblastoma). This is not remarkable in view of the fact that these neoplasms take origin from the vestigial remains of the craniopharyngeal (cranio-buccal) canal. The most recent comprehensive collection and analysis of craniopharyngiomas is that of Frazier and Alpers. They illustrated ameloblastic elements of the primitive enamel organ, but nowhere did they find evidence of true enamel formation. Peet described an irregular "pseudo-enamel" in an adamantinoma of the pituitary body. McLean mentioned "two areas bearing resemblance to an early enamel organ" in a parapineal teratoma.

Neural elements have repeatedly been found in teratomas of the pineal body, both as immature ganglionic structures and as well formed nerve cells and fibrils. Klapproth reported embryonal medullary epithelium in his case of a teratoma of the pineal body. Neuroglia is less common and is reported only by Boehm, Frank and ourselves.

The teratoma in its evolution may destroy the pineal tissue, may include it within its structure or may give rise to pineal tissue as new growth material. Klapproth reported adenomatous hyperplasia of the pineal body as an integral part of the teratoma. The immature pineal tissue so widely dispersed throughout our tumor, though not as abundant or as actively proliferating as in the case of Klapproth, is apparently of the same nature. The intimate association of the pineal and

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6. R. A. C. Rigby has published roentgenograms of a skull showing a suprasellar cyst with shadows which he interpreted as teeth. However, his report is accompanied by neither anatomic nor pathologic data. He cited Bonorden as reporting a tumor of the olfactory area with fourteen teeth. This is evidently an error, as Bonorden's report describes a cyst containing squamous epithelium, hair and sebaceous glands but does not mention teeth.

The thesis is advanced that the impulse for embryonal tumor formation within the pineal body originates in an inherent multipotentiality in the primitive cells of the pineal body similar to that found in cells of the testis and ovary.

The clinical features of embryonal tumors of the pineal body have been reviewed, with especial emphasis given the syndrome known as "macrogenitosomia praecox."

A new case of teratoma of the pineal body is here reported in which a unique feature is the presence of teeth in all stages of development up to the adult forms. Such formations have not been reported in teratomas of the pineal body prior to this time. Similarly unique formations are seen in the extensive development of structures identified with the nasopharynx and with the thyroid gland.

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# METASTASIZING HEMANGIOMA SIMULATING AN ANEURYSM

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Hemangiomas are generally regarded as benign tumors of the blood vessels. Passing reference to a rare form exhibiting malignancy clinically and giving rise to distant metastases is made in most of the standard works on tumors. Isolated cases of this sort have appeared from time to time.<sup>1</sup> Wright<sup>2</sup> in 1928 reported an additional case and reviewed the literature. In the recorded cases the breast, liver, lungs and pleura, intestines, spleen, kidney, heart, adrenal glands and subcutaneous tissues have been involved. Because of the unusual clinical form as well as the rapid recurrence of the tumor and metastasis in spite of intensive irradiation, the following case seems worthy of being placed on record.

## REPORT OF A CASE

An 82 year old white man was admitted to the Johns Hopkins Hospital on March 29, 1936. He had had a small lump in the hypothenar region of his right hand for approximately fifteen years. The lump had been entirely painless and had given him no concern until three months before admission, when it suddenly began to increase in size and became painful. There was a history of trauma. Examination showed an extremely well preserved man of advanced years. On the hypothenar eminence of the right hand there was a rounded swelling 4 cm. in diameter. This mass was tightly attached to the skin and was not movable over the palm, but a definite arterial pulsation was felt. No murmurs were heard. The ulna artery above the tumor was twice the size of the corresponding artery in the left wrist and gave a forceful pulsation. The right ulnar artery was twice the size of the right radial artery. The epitrochlear nodes were not palpable. A small soft gland was palpable in each axilla.

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hard, whitish nodule. The wrist was purple, and a long red streak was observed extending up the flexor surface of the forearm. Aspiration yielded a few drops of blood, but there was no free flow as before operation. Roentgen treatment was commenced, and the mass diminished in size. From June 1 to 6 the patient received 816 roentgens to the right hand. From June 30 to July 8 he received 1,067 roentgens to the right hand and 912 roentgens to the right axilla. There was only mild regression in the size of the tumor. On August 20 the tumor was noted to be three times its original size, and a large mass of hard glands was palpable in the right axilla. The entire hand and wrist were red. The patient died on September 3.

*Description of Surgical Specimen.*—Gross Description: The specimen consisted of a pear-shaped mass of tissue measuring 5 cm. in length and 3 cm. in diameter. Externally it was smooth and dark blue. From one pole a small artery protruded about 2 mm. At the other pole no distinct artery was seen, although there were a few tabs suggesting remnants of veins. On section the specimen was seen to



Fig. 2.—*A*, photographs of the hand before operation. *B*, photographs of the hand four months after operation, showing recurrence of the tumor. Note the red streaks extending up the forearm.

contain blood clot in various stages of organization; that near the center was friable, while more peripherally there were successive laminae of fibrous tissue and blood clot. The wall of this sac appeared to be continuous with that of the artery but was much thinned out. At one point in the center there were small radial streaks suggesting cholesterol crystals.

*Microscopic Description:* Section 1 was prepared and mounted on a large slide in order to show the entering artery. Only a short section of the artery was included, but this much appeared normal. The rest of the mass was composed of numerous endothelium-lined spaces of all sizes and shapes and containing red blood cells. Many of the spaces were linear, while others were cavernous or tortuous.

Section 2 showed a similar picture; the growth was fairly well encapsulated, and several apparently normal arteries of medium size lay on its outer margin. At some points encapsulation was less perfect than at others, but at no point could the vascular channels be traced outside of the main tumor mass. There were some areas which contained small cholesterol crystals. One gained the impression that there had been extensive hemorrhage followed by organization and hyalinization.

Verhoeff-Van Gieson's stain showed small areas in the periphery which contained reticulum. In no place, however, were these fibers really continuous enough to constitute even an aneurysmal wall.

*Autopsy.*—Autopsy was performed four hours after the patient's death.

Attached to the palmar surface of the right hand at its ulnar margin was a large hard tumor measuring 6 by 4 cm. It was adherent to the underlying structures, while the overlying skin showed a bluish discoloration extending up over the wrist for about 6 cm. After this mass was removed it was found to have eroded the fifth metacarpal bone, so that little of the osseous structure remained. On section the mass was seen to contain many spaces filled with blood, a good part of which had clotted; whitish areas or strands resembling fibrous tissue were also observed. The tumor did not seem to have a definite capsule except where it was attached to the skin. At this point a few muscles were adherent. On the flexor surface of the forearm, extending upward toward the elbow, was a fibrous band about 1 mm. in diameter. This lay directly beneath the skin and became more medial, until at the bend of the elbow it lay on the medial aspect and was attached to the firm epitrochlear gland. On section the gland was found to resemble the tumor below. Extending from the epitrochlear node upward to the axillary lymph nodes was another firm cord of the same type. The axillary nodes were considerably enlarged, measuring about 3 by 4 by 4 cm., and were apparently replaced by the same kind of tumor. These nodes were adherent to the axillary vessels and also to the ribs, but the tumor did not seem to have invaded the latter. There was no sign of intrapleural extension.

The heart weighed 550 Gm. There was marked coronary sclerosis. The chambers were dilated. Numerous small gray scars were seen in the myocardium.

The gallbladder contained twenty-five small cholesterol stones. At one point near the fundus the wall was thickened and firm, resembling a carcinoma. One firm node was found near the head of the pancreas.

The aorta was sclerotic and tortuous.

Other organs showed no significant changes.

*Microscopic Notes:* Sections from the hand showed the tumor to be covered by dense keratinizing epithelium, which was hyperplastic. Fresh hemorrhage, thrombotic material and polymorphonuclear leukocytes were widespread. The same blood spaces were seen as were found in the surgical specimen, but the lining cells were more dense and deeply staining. In places they were almost round. These had more oval nuclei, were vesicular and contained prominent nucleoli. Their cytoplasm was rather voluminous and did not tend to merge with that of the nearby cells. No definite mitotic figures were seen. There was no evidence of blood clot formation. In places the angiomatous structures showed active invasion of the surrounding tissues. A great deal of scarring and necrosis was evident. A section from the fifth metacarpal bone showed active destruction and fragmentation of the bone into small spicules.

The mass in the epitrochlear node showed bands of cells infiltrating between muscle bundles and replacement of the lymphoid tissue by tumor. However, there was no formation of blood spaces. The axillary nodes were almost completely replaced by tumor cells. Here there was a distinct tendency to the formation of vascular channels. The prussian blue reaction demonstrated a large amount of iron pigment. One of the large nerve trunks was completely surrounded and compressed by tumor.

The gallbladder and pancreatic node showed typical adenocarcinoma.

# A REVIEW OF UROLOGIC SURGERY

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## KIDNEY

*Anomalies.*—Geisinger<sup>1</sup> stated that supernumerary kidney has remained so rare that its discovery has been carefully recorded in most instances and has led to several diligent consultations of records. Thirty-eight cases of true supernumerary kidney, reasonably authenticated, are reported in the world's literature. To this number Geisinger added 2 cases, bringing the total to 40.

The accessory organ may be equal in size, and presumably in function, to its mate. In an occasional instance it has been larger; usually it is smaller and occupies a functional status equivalent to that of the ordinary hypoplastic kidney. Not infrequently the histologic detail may be considerably disordered; more generally it is comparable to that of the normal kidney. The vascular distribution varies to an extent that makes it profitless to attempt any description. The relationship of the associated ureters is more particular and more interesting and also of more practical consequence. Probably in a majority of cases the ureters become fused at some point, often near the bladder, so that only the usual two vesical orifices are present; in a number of cases, however, complete duplication exists, and either there are three orifices in the

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1. Geisinger, J. F.: Supernumerary Kidney, *J. Urol.* **38**:331-356 (Oct.) 1937.

Sisk and Kundert<sup>3</sup> reported 2 cases of duplication of the lower part of the ureter with one ureter ending blindly. This condition is a developmental anomaly. There are two theories set forth to explain this type of duplication: premature or exaggerated cleavage of a single ureteral bud or the occurrence of duplicated ureteral buds arising from the wolffian duct.

Characteristic symptoms do not occur with this condition. In both of the cases reported in this paper hematuria was the important symptom. One patient suffered a mild degree of pain; the other experienced no pain.

Neither an excretory urogram nor the usual retrograde pyelo-ureterogram will reveal such ureters, except when the ureteral catheter enters the ureter which has the blind ending, as in the first case. When this occurs, a retrograde injection will, of course, show the ureter with the blind ending, and the normal pelvis will be shown by the excretory urogram. Use of the retrograde pyelo-ureterogram made with a large catheter or bulb just within the ureteral orifice is the method of choice and is most likely to reveal the condition.

*Resection.*—Goldstein and Abeshouse<sup>4</sup> reviewed the literature on resections of the kidney and collected reports of 290 cases in which this operation was performed and added reports of 6 personal cases.

Partial resection of a kidney is the operation of choice in the treatment of the following localized diseases of the kidney: solitary serous or hemorrhagic cysts; hydatid cysts; localized hydronephrosis or pyonephrosis, with or without renal calculi; benign tumors; localized cortical abscesses; renal carbuncles; renal infarct, and renal fistula. Partial resection of a kidney is contraindicated in the treatment of tuberculosis or malignant tumors of the kidney in the presence of a healthy kidney on the opposite side. Partial resection is occasionally indicated in the treatment of extensive bilateral disease, such as tuberculosis, calculous pyonephrosis and rupture of the kidney. Under such circumstances, it becomes an operation of necessity.

In operations requiring extensive reduction of the total kidney substance (the removal of one kidney and from a half to a third of the other kidney or bilateral resections) it is advisable to perform the operations in two stages with an interval of at least four to eight weeks between operations. The minimal amount of renal substance necessary to maintain life in man is one fourth of the total renal substance (one half of one kidney).

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3. Sisk, I. R., and Kundert, Palmer: Duplication of the Lower Ureter Ending Blindly. *J. Urol.* **38**: 261-266 (Sept.) 1937.

4. Goldstein, A. E., and Abeshouse, B. S.: Partial Resections of the Kidney: A Report of Six Cases and a Review of the Literature, *J. Urol.* **38**:15-42 (July) 1937.

In removing segments of anatomically normally formed kidneys, if an aberrant vessel is found one may clamp it off, accomplishing much the same purpose as when one is dealing with a double kidney; however, it is often necessary to amputate the segment to be removed without ligating the vessels supplying blood to the segment.

In the author's series of cases there was no immediate mortality. One of the patients on whom heminephrectomy was performed for horseshoe kidney died of metastasis a little over a year after operation. In another case calculous nephrosis developed in the remaining half of the kidney, but the patient was living twelve years after the primary heminephrectomy. There were no deaths following any operations on double kidneys or on anatomically normally formed kidneys. All of the patients were reexamined, and at the time Hess' report was written they were comparatively free from the symptoms which brought them to the clinic.

*Hydronephrosis.*—Smagghe<sup>6</sup> discussed the opinions expressed by various operators in regard to the treatment of hydronephrosis. He reported 12 cases and stated that bilateral hydronephrosis is comparatively common. The frequency of this condition is brought out by more universal use of intravenous pyelography. Infection and calculi are seen frequently in association with hydronephrosis and are due to stasis of the urine and alteration in the urinary acidity.

Radical treatment was carried out only when the opposite side proved to be normal. Drainage of one kidney is advisable in some cases of hydronephroses when extensive involvement of the opposite side makes conservative treatment necessary.

Pilcher<sup>7</sup> reported a case of bilateral congenital hydronephrosis in a woman aged 38 which demonstrated several points of importance in the conservative treatment of this condition.

On the left side large anomalous vessels which could not be severed were found running to the lower pole. The pelvis was resected, and the ureter was reimplanted anteriorly to the vessels. On the right side a definite ureteral stricture was found extending below the ureteropelvic junction. The pelvis and the strictured area of the ureter were resected, and the ureter was reimplanted in the remaining portion of the pelvis. In both instances a nephrostomy tube was inserted, and a soft rubber catheter was passed through the lower calix and down into the upper portion of the ureter. This catheter, used as a ureteral splint, was removed ten days after the operation. Subsequently, on each side, it was found that when the nephrostomy tube was clamped the patient

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6. Smagghe, H.: Les hydronéphroses bilatérales, *J. d'urol.* **43**:5-33 (Jan.) 1937.

7. Pilcher, Frederick, Jr.: The Treatment of Bilateral Congenital Hydro-nephrosis, *Proc. Staff Meet., Mayo Clin.* **12**:279-282 (May 5) 1937.

edge if there are two well functioning kidneys. But when only one kidney is working and the ureter becomes clogged with gravel to the point of complete obstruction, the result is anuria accompanied by severe renal colic.

The same results follow if the renal pelvis and the calices become similarly packed with gravel or what may be called a mud pack. It can be readily understood that under the influence of a water cure or of certain diuretic medicaments this clogging may be resolved by the gradual elimination of the gravel. This occurred in the case of a young girl whose roentgenograms, taken eight months apart, showed in the first what appeared to be a large coraliform stone and in the second a calculus only the size of a small bean. This patient reported that two or three months previous to the second roentgen examination she had experienced a severe attack of renal colic, followed by spontaneous elimination of a large amount of urinary gravel. Thus it was evident that the supposed coraliform stone had not been a stone but was a large mass of gravel.

Cases of this kind are not frequent and appear to be rather little known to urologists. Much more common are cases in which true lithiasis is accompanied by masses of gravel within pyonephritic pockets.

Raising the question whether one can recognize these masses in the roentgenogram, Marion stated that it is not always possible. If an entire ureter appears opaque, one may think of such a condition; but more frequently this is not the case, and gravel is not considered. If gravel is in the renal pelvis and the contour is a little indistinct, not so sharp or so well defined as that of a calculus, one may likewise suspect such a condition. In two roentgenograms the images indicated something less compact than a stone, which might well orient the diagnosis in the right direction. But unless this is the case, it is impossible to foresee the existence of an agglomeration of gravel in advance of operation. However, this is not of capital importance, for if there is anuria, whatever the cause, ureteral catheterization without delay is the proper recourse, and this will usually open the ureter blocked with gravel. If, on the other hand, the pelvis is packed with gravel that resembles a calculus, the indication for operation is absolute, no matter whether gravel or a true calculus is present.

Discovery of the etiology of urinary calculus is essentially a urologic problem. For the past seven years Randall and Melvin<sup>11</sup> have been interested especially in the problem of the etiology of primary renal calculi and have repeated in experimental studies, 'in one form or another, most of the conditions theoretically productive of stone. They have a firm conviction that there has to be an initiating lesion in the

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11. Randall, Alexander, and Melvin, P. D.: The Morphogeny of Renal Calculus, *J. Urol.* **37**:737-745 (June) 1937.

Microscopic sections have been made through the plaques of calcium in the walls of the renal papillae. Study of these sections has shown that the first deposit is regularly within the papilla and not on its surface. It is not the familiar intratubular cast but spreads out through the interstitial tissue as a definite morbid process and deposit. The most important fact to be observed is that this primary calcium deposit is definitely beneath the surface and is noninflammatory.

There is evidence that as such a calcium plaque increases in size the covering epithelium loses its support and nutrition, and the plaque is denuded gradually of the epithelial tissue covering it.

One kidney gave evidence of three papillae with the simple calcium deposit, but on a fourth papilla there was a characteristic crystalline calculus growing directly on a calcium plaque. This calculus was approximately 2 by 3 mm. in size, of brownish tint and firmly attached.

An important fact is again pointed out: In none of the foregoing cases was there the slightest evidence of an infection or of an infectious process, contrary to generally accepted opinion; this holds true for numerous slides of similar lesions that have been subjected to microscopic study.

*Tuberculosis.*—Klasson<sup>12</sup> compared a series of 42 cases of renal tuberculosis in children under 16 years of age observed by Wildbolz with a series of cases of tuberculosis in adults. He concluded that the disease is fairly common in children. In the first ten years of life it is found rarely but increases in frequency rapidly after this time, until, at the end of the second decade of life, it is as common as in the third decade. Bilateral renal tuberculosis is found twice as often in children as in adults, but its origin, as in adults, is apparently unilateral in most instances.

The pathologic process in children is similar to that occurring in adults. Although genital tuberculosis in male children is less frequently seen in association with tuberculosis of the urinary tract than it is in later periods of life, in the majority of children having tuberculosis of the urinary tract tuberculous foci are also found in other organs, such as the lungs and bones. The symptoms, treatment and prognosis are the same in children and adults.

*Tumors.*—Mathé<sup>13</sup> expressed the belief that nephrectomy is still the treatment of choice in cases of carcinoma of the kidney. Irradiation is of value but should not supplant surgical removal. Preoperative irradiation is of value in producing regression of huge growths, thereby rendering certain inoperable tumors operable. Postoperative irradiation

12. Klasson: Ueber die Nierentuberkulose bei Kindern, Ztschr. f. urol. Chir. u. Gynäk. **43**:194-201, 1937.

13. Mathé, C. P.: Cancer of the Kidney: Present-Day Status of Its Treatment and End-Results, California & West. Med. **46**:385-390 (June) 1937.



tively. The causes usually given were shock and hemorrhage. At the time the author's report was written, 21 patients were living, 15 for less than one year. Six had passed the first year, 3 of whom had lived beyond the five year period. Of these 3, 1 had lived twenty years, but the histologic diagnosis of sarcoma seemed to be in doubt. Five patients underwent an exploratory laparotomy. Of these, 2 died post-operatively, and necropsy revealed evidence of multiple metastases. The condition in 3 was found to be inoperable.

Caulk<sup>15</sup> stated that with few exceptions tumors of the renal pelvis are epithelial, the majority being of the papillary variety. According to authorities, papillary tumors constitute about three fourths of the growths in the renal pelvis.

Papillary tumors have a tendency to be multiple and occur more frequently in men than in women. On the other hand, squamous cell and other invasive tumors occur in about the same proportion in men as in women. The papillary tumor possesses the notorious quality of involving other parts of the urinary system, particularly the ureter and the bladder on the corresponding side and occasionally the opposite ureter, either simultaneously or with recurrences. This occurred in 50 per cent of cases. The infiltrative squamous growth lacks this trait. This decided difference has a definite bearing on the type of surgical procedure. After removal of a kidney for pelvic tumor, a gross pathologic examination should be made, and in case the tumor is papillary, nephroureterectomy with partial resection of the bladder is necessary, otherwise nephrectomy will suffice.

The papillary tumor is slow in progress and is not nearly as malignant as the nonpapillary tumor. It is seldom associated with any preexisting pathologic factors, such as stone or leukoplakia, whereas the nonpapillary growth is decidedly malignant and occasionally is associated with stone, infection or leukoplakia. As a rule, the associated tumors are similar in their histologic structure to the neoplasm of the pelvis.

The diagnosis of pelvic tumor is made chiefly by urographic study. The majority of tumors are associated with profuse hematuria; rarely is there a palpable renal tumor, except in instances of hydronephrosis or hematonephrosis. Renal pain has been common in all cases reported and usually results from pelvic block, with resulting pyelectasis. Urographic evidences of filling defects in the pelvis and ureter may again be deceptive and may not represent neoplasm. Intravenous urography may be of assistance to the diagnostician in certain cases, but delineation

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15. Caulk, J. R.: Tumors of the Renal Pelvis and Ureter, *Ann. Surg.* 106:68-84 (July) 1937.

Kimball and Ferris stated that a method of treatment should be chosen which would remove the disease in its entirety.

Several technics have been proposed; the most favored at present and the one which to Caulk is unquestionably the most satisfactory is nephro-ureterectomy by a combined lumbar and lower midline exposure.

Priestley<sup>17</sup> stated that primary squamous cell tumors of the renal pelvis are of two types, papillary and nonpapillary. Both are relatively uncommon, the nonpapillary variety being quite rare. Differentiation of these two types of tumors is of importance because they differ clinically, pathologically, prognostically and in the procedure of choice best adapted for their surgical approach. The papillary tumor is usually lower in grade of malignancy, runs a slower clinical course and metastasizes by implantation into the ureter and the bladder. Generally speaking, if not too far advanced, this growth offers a reasonably good prognosis when treated by nephro-ureterectomy with removal of the adjacent bladder. On the other hand, the nonpapillary variety tends more often to run a rapidly fatal course. Pathologically, such a growth appears of a higher grade of malignancy. The growth occurs by extension into the kidney and its surrounding structures and by the occurrence of distant metastasis. Nephrectomy, with removal of a relatively short portion of the adjacent ureter, suffices, since metastasis does not occur by distant implantation in the ureter and bladder. Postoperative longevity seldom has exceeded nine months.

*Renal Operations.*—Goldstein<sup>18</sup> reported a series of 43 (12.5 per cent) accidents occurring in 345 operations on the kidney. Eight patients (20 per cent) died, 4 from hemorrhage. Hemorrhage was responsible for 49 per cent of the serious accidents. Nine kidneys were sacrificed because of uncontrollable hemorrhage, but in these instances there were no deaths. In 3 patients bleeding came from the injured aberrant vessels; in 2, from injured retropelvic vessels, and in 4, from the kidney proper. Goldstein stated that all bleeding should be controlled before the patient leaves the operating table. Clamps should be left on the pedicle without hesitation when necessary. The clamps should be placed with great care. Opening of the diaphragm, the pleura or the peritoneum is not a serious accident. If possible, such rents should be closed, but the renal bed should be drained. Opening of any part of the intestinal tract is a serious accident, and closure should be done immediately. Fracture of a rib or division of a nerve is not a serious accident; nature will take care of such injuries.

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17. Priestley, J. B.: Non-Papillary Squamous Cell Epithelioma of the Renal Pelvis, *J. Urol.* **37**:674-679 (May) 1937.

18. Goldstein, A. E.: Accidents in Renal Surgery, *Surg., Gynec. & Obst.* **65**: 515-522 (Oct.) 1937.

secreted was compared with that of the urine secreted from the opposite kidney, which was under normal conditions of pressure.

The results of this study indicate that the kidney will secrete urine that is normal in quantity and composition against pressures up to and including one of 30 cm. of water. At pressures of 40, 50 and 60 cm. of water there is a regular diminution in the volume of urine and often a greater diminution in the total amount of chloride. There is no change in the total amount of creatinine and urea at pressures less than 60 cm. At a pressure of 60 cm., a slight diminution in the total amount of creatinine and urea begins to occur. The excretion of phenolsulfonphthalein is first diminished at a pressure of 35 cm., and a progressively decreasing output occurs as the pressure is increased.

Causing the kidney to secrete against pressures up to and including 60 cm. of water for one hour did not affect the function of the opposite kidney, nor was a significant anuria or polyuria of either kidney ever observed.

In those instances in which unilateral infection of the kidney occurred, the infected organ excreted the larger quantity of urine and chloride, whereas the healthy kidney excreted almost the entire quantity of creatinine, urea and phenolsulfonphthalein.

Hortolomei, Burghel and Streja<sup>21</sup> stated that it is now assumed universally that the upper part of the urinary tract must be considered as a complex apparatus, assuring evacuation by its functioning, and not, as was formerly believed, just a tubular system through which the urine flows toward the bladder. The present day knowledge with reference to innervation of the organs of the vegetative nervous system enables one to affirm that the tonicity of the urinary tract is maintained by the sympathetic nervous system and its motor functions are maintained by the parasympathetic nervous system.

The modern notion of the functional unity of the ureter has been arrived at by clinical observation, aided by intravenous urography. The urinary tract, both topographically and functionally, is divided into two portions, one portion being devoted to the transportation of the urine (pyelo-ureteral tract) and the other to its collection in a reservoir (bladder) with a draining canal (urethra). The upper part, which is the active part of the urinary apparatus, must continually adapt itself to the work it has to do. The functional modifications that have this end in view are uniformly the same throughout the entire length of the conduit, from one end of the excretory tract to the other. In a normal conduit they are never localized predominantly or exclusively in one segment.

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21. Hortolomei, N.; Burghel, T., and Streja, M.: *Considérations sur la physiopathologie des voies urinaires supérieures*, J. d'urol. **43**:399-429 (May) 1937.

and yet their functional existence is beyond dispute if the pelvis is watched emptying itself under the fluoroscopic screen.

When diuresis increases, the tone of the excretory canal is lowered. But if one assumes that this physiologic hypotonia is unequal, or that its effects are unequal at different points of the canal, all is easily explained. The most tonic portion lets the wave pass only at the moment of systole, when the force of propulsion from the pelvis overcomes its tone. Evacuation occurs at that moment in the manner described by Legueu, who observed it by means of the pyeloscope. When diuresis again becomes moderate, the pyelic tone returns to its normal level, and presently there is nothing to differentiate functionally the pelvis and the ureter from "these sphincteral regions."

Hormonal influences appear to exert some action on the functioning of the upper part of the urinary tract, especially the influence of the hypophysis. To accomplish normal functioning of the urinary apparatus, two conditions are necessary: (1) functional integrity of its dynamic elements and (2) anatomic integrity of the pathways of evacuation, assuring a free outlet for urine. The commonest dynamic disturbances from exaggeration of function are hypertonia and hyperkinesia, which provoke colic. That patients with such a disturbance of function suffer with a local neurovegetative disequilibrium has been recognized, especially in America, where cure has been effected by suitable neurologic treatment.

On the other hand, there are dynamic difficulties owing to diminution of function, better known as hypotonia, hypokinesia and atony. Primary hypotonia results most commonly from infection, and from the start it paralyzes or diminishes the capacity of the conduit for reaction to its disturbances with respect to urinary evacuation. Some of these cases are of endocrine origin and some are congenital.

Whenever a primary hypotonia of dynamism accompanies or precedes a disturbance provoked by a mechanical obstacle, urinary stasis is more marked than it would be if either factor were present alone. Examples of this are found in uterine pressure, which aggravates the hypotonia of pregnancy, and in infection, which increases stasis in the presence of ureteral calculi.

*Renal Osteitis Fibrosa.*—Albright, Drake and Sulkowitch<sup>22</sup> reported a case of a condition termed "renal osteitis fibrosa generalisata" and included the results of postmortem examination. Two similar cases are cited. The characteristics of the disease are long-standing severe renal insufficiency, marked retention of phosphate, a normal or low level of serum calcium, severe acidosis, arteriosclerosis, calcium deposits

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22. Albright, Fuller; Drake, T. G., and Sulkowitch, H. W.: *Renal Osteitis Fibrosa Cystica: Report of a Case with Discussion of Metabolic Aspects*, Bull. Johns Hopkins Hosp. 60:377-399 (June) 1937.

lows: In first type the communicating calix appears somewhat drawn out and rigid. It terminates abruptly at the rim of the calcified ring, showing neither diminution in bore nor dilatation. In the second type the calix does not terminate abruptly but ends in a crescentic or cup-shaped shadow on which the circular calcified ring rests like an acorn in its cup. In the third type the flamelike areas of shadow pass out into the area bounded by the circular calcified ring, and a definite circumferential ribbon of shadow may appear reenforcing the latter. In the fourth type, in rare cases, the flamelike or circumferential shadows may pass out directly from the abrupt termination of the calix, the crescentic area being absent.

In cases of open hydatid cyst the pyelographic appearances are quite characteristic, especially if an adequate amount of fluid is injected and the injection continued to the point where the patient feels the discomfort of pressure. The crescentic bulge then becomes continuous, with a dense shadow which is well defined and circular, and represents the cyst cavity proper. In cases, however, in which numerous and closely packed daughter cysts are present, little fluid runs in except in irregular patches, more particularly around the rim.

In cases in which there is no communication between the cyst and the pelvis, the appearances are not so characteristic. The pyelogram is similar in many cases to that produced by a solitary cyst or even by a tumor. The kidney may be displaced, complete calices may be obliterated by pressure and the ureter may be pushed inward toward or even across the vertebral column. Sometimes a cyst may push itself into the angle between two of the major calices, separating them in such a way that they form a right angle with each other.

The characteristic pyelographic appearance of a cyst in the calix is the presence of well defined minor calices separated from the lumen of the major calix by a filling defect representing the parasite, with or without flamelike shadows connecting the two.

In practice, pyelography is chiefly of value in determining the side, site and nature of an open cyst that has already been diagnosed by identification of hydatid material in the urine, or in cases of closed or pseudo-closed cysts, in which the typical ring shadow seen in the roentgenogram may indicate a lesion of the spleen, liver or kidney or a pararenal cyst.

*Aneurysm.*—McKay<sup>25</sup> reported a case of true aneurysm of the renal artery, the diagnosis having been made at operation when the sac ruptured as the pedicle of the kidney was being isolated. The occurrence

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25. McKay, R. W.: True Aneurysm of the Renal Artery, *J. Urol.* **37**:783-789 (June) 1937.

number of erythrocytes per cubic centimeter of blood in the experimental animals fell rapidly during the first three or four days and remained low until about the thirteenth day, when it slowly rose again. In the control animals, in which the kidney was exposed but not traumatized, the number of erythrocytes was in no way modified. The number of leukocytes in both groups underwent considerable variations, usually in inverse ratio to the erythrocyte count but without any precise significance being discernible. It is impossible to state whether the anemia was due to toxic destruction of the kidney or to diminished hematopoiesis. Clinical findings of certain authors suggest the possibility that degenerative modifications of the kidney produce some toxic agent capable of exerting an unfavorable influence on the number of erythrocytes. The authors emphasized the importance of making frequent reexaminations of the blood after traumatism of the kidney has occurred.

With reference to treatment, injuries of types 1 and 2 can be handled expectantly; they seldom are seen by the surgeon, since hematuria is negligible. Those of type 3 as a rule require surgical intervention, but the tendency today is toward conservative intervention, which has become the rule since pyelography has made exact preoperative diagnosis possible. About two thirds of renal injuries are susceptible to conservative treatment. In cases of grave lesion with the urographic picture of rupture of the renal pelvis, with persistent hemorrhage and a state of shock, with lowered blood pressure and with a lowered erythrocyte count, conservative treatment with reparation of the ruptured tissue and drainage will in many cases secure restoration of function to the kidney. Transfusion of blood may be necessary, with recourse to the injection of serum, the application of artificial heat and the administration of sedatives. Plenty of time should be allowed for these measures before one resorts to nephrectomy. It should be thoroughly understood that surgical intervention in these cases does not necessarily imply nephrectomy but allows the surgeon to arrest hemorrhage and to repair, drain and conserve the kidney. In injuries of type 4, however, the only treatment possible is usually nephrectomy.

*Ureteropyelic Dynamism.*—Franché, Falcoiano and Chipail<sup>27</sup> made an exhaustive experimental study of ureteropyelic dynamism, as the result of which they reject as erroneous certain ideas that have recently been put forward by other authors on the subject. Notable among these ideas is the view that sympathectomy, whether by knife or by chemical means, can lead only to pure disturbances of dynamism in the ureter and pelvis, without producing any mechanical obstruction.

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27. Franché, O.; Falcoiano, N., and Chipail, G.: Le problème expérimental due dynamisme urétéro-pyélique, *J. d'uroi.* **43**:430-438 (May); 501-513 (June) 1937.

and of functional pyelic retention. These disturbances varied in the different examinations and sometimes even during the course of one and the same examination. 3. Sometimes these disturbances of dynamism may be altogether wanting after a sympathectomy correctly executed and followed by a characteristic ureteropyelic dilatation.

#### AMICROBIC RENAL PYURIA

Schaffhauser<sup>28</sup> discussed amicrobic renal pyuria based on studies of literature (19 personal cases observed at Professor Clairmont's clinic in Zurich and in Professor Wildbolz' clinic in Berne) and on experimental work. Views on amicrobic renal pyuria have changed in recent years. The occurrence of amicrobic urine in connection with renal tuberculosis is not uncommon. Separated urine, sterile on common culture mediums, was usually considered pathognomonic for tuberculosis, but such deductions are not necessarily true.

It has been ascertained by clinical, bacteriologic and histologic evidence that there exists a purulent disease of one or both sides of the upper part of the urinary tract, with accompanying serious cystitis, mostly without fever and of great chronicity, in which neither a direct smear nor an aerobic or anaerobic culture discloses microbes and in which a tuberculosis of the urinary tract can be excluded. Scandinavian authors (Söderlund, Galtin, Runeberg and Troell) were the first to report on nontuberculous amicrobic pyurias. Schaffhauser's 19 personal cases show such a conformity with Söderlund's cases that amicrobic pyuria can be accepted as a pathologic entity. The etiology of the disease is as yet not fully known. Schaffhauser expressed the belief that in some cases an atypical streptococcic infection may be the etiologic agent. In some instances streptococci could be cultured on Rosenow's broth. In 3 cases inoculation of purulent urinary sediment of patients having amicrobic pyuria into the renal pelvis of dogs caused chronic streptococcic pyelitis. It is important to know that unilateral amicrobic pyuria occurs, because in not a few instances kidneys have been erroneously removed when tuberculosis was thought to be present. The therapy of choice for amicrobic pyuria is the injection of small doses of arsphenamine. In every one of the patients so treated in a series reported by Wildbolz, recovery was rapid and definite.

To be distinguished from amicrobic pyuria are the amicrobic stages of acute or chronic infections of the kidney or renal pelvis, in which the original microbe can be found only after repeated cultures or sometimes not at all. The etiology of these cases is not uniform.

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28. Schaffhauser, F.: Die sogenannten abakteriellen renalen Pyurien, *Ztschr. f. urol. Chir. u. Gynäk.* **43**:83-140, 1937.

stone. By active manipulation is meant passage of instruments which actually grasp the stone and withdraw it; for instance, one may pass several ureteral catheters beyond the stone, twisting them so as to enmesh it and then withdraw it, or one may pass various types of ureteral stone extractors to engage the stone and withdraw it.

The passive type of manipulation is not difficult to perform and seldom presents technical difficulties to the surgeon, but it also is seldom efficient unless the stone is small and the patient is willing to endure repeated attacks of colic over varying periods of time before the stone is finally passed or removed by open operation. The active type of manipulation is successful in a high percentage of cases if done skillfully and with great care. However, if painstaking technic and the utmost gentleness are not exercised, serious difficulties and complications may ensue.

With regard to the size of the stone, Thompson emphasized repeatedly a rule to follow; he stated that the deciding factor is not the size of the stone but rather the diameter of the ureter, and he insisted that no stone should be manipulated if there is not sufficient room in the ureter. One method of deciding this point is by the preliminary passage of ureteral catheters alongside the stone. It should be possible to pass two no. 5 ureteral catheters easily beyond the stone before passage of the stone extractor is attempted. When the extractor is passed, it should be passed gently and should never be forced. If these factors are kept in mind, a minimum of difficulty will be encountered.

Even though these rules are adhered to, however, a third difficulty may be encountered. This is the possibility that the stone may become arrested somewhere in the ureter in the course of its withdrawal. This is a rather uncommon occurrence, but it does happen often enough to be important. One must be careful not to exert too much traction in such a case or injury to the ureter may occur. Such a situation presents a real problem to the surgeon and may necessitate ureterolithotomy. Occasionally stones enmeshed in the stone extractor became arrested at the ureterovesical junction and were removed successfully by means of a two stage procedure without undue trauma or resort to open operation.

In 1 case two no. 5 ureteral catheters passed easily beyond the stone. The Councill stone extractor was introduced into the ureteral meatus, and the wires were expanded to dilate the intramural portion of the ureter. Then the extractor was passed easily beyond the stone, which was engaged readily. As it was being withdrawn, it became arrested at the proximal end of the intramural portion of the ureter and could not be removed. A roentgenogram made at this time revealed the stone enmeshed in the basket of the extractor in this position. In spite of



allowed to remain in contact with the pelvis and ureter approximately fifteen minutes. After this the instruments are withdrawn, at which time they are slowly twisted and more solution is injected directly into the lumen of the ureter, thus insuring a more adequate perfusion of the ureter with the solution. The patient is instructed to void in the erect posture.

Of 27 consecutive cases in which multiple catheters and instillations of this solution were used, the calculus was recovered in 25 (92.5 per cent). In 13 cases (48.1 per cent) the stone was recovered as soon as the patient voided.

#### PROSTATE

*Hypertrophy.*—Thompson<sup>32</sup> reported 2 cases in which unusual intravesical projection of the enlarged prostate gland was evident. Until recent years such enlargements were of little interest to urologists, for they were easily enucleated during the course of suprapubic prostatectomy. In contrast, such projections are now sometimes difficult to remove by transurethral resection and often one is overlooked and results in persistent symptoms and unsatisfactory vesical function. Bizarre filling defects are sometimes noted in the cystogram, and at times granulation tissue is superimposed on the enlargement and is mistaken for vesical neoplasm. Thorough removal of all intravesical prostatic tissue during the course of transurethral resection is essential to a good result.

Clarke<sup>33</sup> stated that interest in the old theory that prostatic hypertrophy is caused by some abnormality of the endocrine system is being revived by the recent isolation of androgen and by the experimental work on prostatic enlargement which this discovery permits. Much of this work is unconfirmed, and some of it is contradictory. According to the theory advanced at the Cleveland Clinic, prostatic hypertrophy is caused by diminution in testicular output of a substance which is designated by McCullagh and his associates<sup>34</sup> as inhibin. This water-soluble substance restrains the output of gonadotropic principle from the pituitary gland, which in turn stimulates the formation of fat-soluble androgen in the testes. Excess of the latter is supposed to be responsible for prostatic stimulation and hypertrophy. Therefore a commercial preparation known as "contruin," said to contain this water-soluble

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32. Thompson, G. J.: Unusual Intravesical Projection of the Enlarged Prostate Gland, *J. Urol.* **37**:367-371 (March) 1937.

33. Clarke, Ruscoe: The Prostate and the Endocrines a Control Series, *Brit. J. Urol.* **9**:254-271 (Sept.) 1937.

34. McCullagh, R. D.: Dual Endocrine Activity of Testes, *Science* **76**:19 (July 1) 1932. Lower, W. E.; McCullagh, D. R., and Walsh, E. L.: Further Report on the Hormonic Control of Prostatic Function, *Tr. Am. A. Genito-Urin. Surgeons* **27**:15, 1934.

The term "cure" cannot be used in describing the progress of these patients. Therefore the term "improvement" is substituted, and this is based on the progress of the symptoms. In no case was there any evidence of actual shrinkage of the gland. Of the 67 patients in groups 1 and 2, the condition in 47 improved and in 10 it was stationary for an average duration of 3.58 years. Of the 26 patients in groups 3 and 4, the condition in 15 improved and in 8 it was stationary for an average duration of 2.64 years. A more detailed classification based on both symptoms and objective signs of the disease is shown in the accompanying table.

These figures show how easily one might be misled in interpreting the results of endocrine therapy. A large number of patients who have prostatic disease can be relieved for a variable period by general hygiene, massage, heat or instrumentation. A large number in this series showed a sustained improvement after instrumentation alone (cystoscopy).

*Detailed Classification of the Course of the Disease (from Clarke)*

Course	Groups I and II	Groups III and IV	Total
(a) Rapid sustained improvement.....	14	2	16
(b) General improvement .....	7	2	9
(c) Improved, with remission.....	15	8	23
(d) Improved, later progressive.....	12	6	18
(e) Slowly progressive .....	11	1	12
(f) Gradually progressive.....	6	6	12
(g) Rapidly progressive .....	2	1	3

Therefore, control series are desirable before any evaluation of the efficiency of endocrine therapy is made, and patients so treated should be studied for a considerable period, not less than five years.

Middleton<sup>35</sup> reported the removal of a prostate weighing 557 Gm. from a patient aged 72. This enormous prostate was almost a pound heavier than the greatest mass of tissue ever removed transurethrally up to now, even with multiple operations. Middleton advised deliberate fragmentation of huge prostates as the easiest, safest method of operation.

This is the largest prostate ever removed surgically. The only larger gland described in medical literature was that reported by Douglas, which weighed 673 Gm. In his case, however, the patient failed to survive suprapubic cystotomy, and the prostate was obtained and studied at necropsy. Freyer, of England, in 1908 removed a prostate weighing 529 Gm., which was the largest surgical specimen previous to the present case.

35. Middleton, R. P.: How Large Is the Hyperplastic Prostate? Report of the Largest Hypertrophied Prostate Ever Surgically Removed, J. A. M. A. 108: 1967-1968 (June 5) 1937.

Memorial Hospital by a single surgeon and were interpreted by a pathologist of long experience in the diagnosis of cancer, who had already examined more than 5,000 specimens obtained by aspiration from tumors in other parts of the body. In the second series, consisting of 50 cases, the specimens were also obtained at the Memorial Hospital by the same surgeon and were interpreted by the same pathologist, the study being begun about six months after the completion of the first investigation. The results reflect the value of experience with this method. In the third series, consisting of 36 recent cases from the service of Dr. Keyes at the New York Hospital, the specimens were obtained by 7 different resident and attending surgeons who were attempting to learn the technic by routine biopsy of all persons admitted with prostatism.

Diagnosable tissue was obtained in 39, or 78 per cent, of the cases in the first series, and no tissue was found in 11. Of the 39 cases in which tissue was obtained, a positive diagnosis of cancer of the prostate was made in 28. No cancer was found in 11. Twenty-seven of the 28 patients with a diagnosis of cancer of the prostate died, and at the time the report was made 1 patient was alive and without evidence of active disease. In the 11 cases in which tissue was obtained by biopsy and in which no cancer was found, no patient was subsequently proved to have cancer of the prostate.

Diagnosable tissue was obtained in 43, or 86 per cent, of the cases in the second series, and no tissue was found in 7. Of the 43 cases in which diagnosable tissue was obtained, a positive diagnosis of cancer was made in 31. Thirty of the 31 patients with a diagnosis of cancer subsequently died of disease, and 1 was alive at the end of thirty-four months but had demonstrable metastasis. In none of the 12 cases in which diagnosable tissue was obtained but no cancer found was cancer of the prostate subsequently proved.

In the third series of cases, in which aspiration biopsy was carried out by surgeons and pathologists of no previous experience with the method, diagnosable tissue was found in 27, or 77 per cent, of the cases, and no tissue was found in 9. Of the 27 cases in which tissue was obtained, a positive diagnosis of cancer was made in 10. Nine of the patients were subsequently proved to have the disease, while 1, on the basis of clinical behavior, was considered not to have cancer.

Treatment of early cancer of the prostate by cystotomy and retrograde instrumental implantation of gold seeds of radon was devised after a study of the biologic effect of different applicators of radium on the tissues in 50 cases of cancer of the prostate in which autopsy was later performed. With this method of treatment, the bladder is opened under spinal anesthesia, and the trigon and neck of the bladder

the bladder had to be opened, such as in cases of stone in the bladder, diverticulum, marked gross infection, etc. There is no indication for transurethral removal after the bladder has been once opened, except in cases of carcinoma, fibrous bars, small fibrous prostates and such obstructions in which suprapubic enucleation would be difficult. In these cases resection should be done anyway. The greatest trouble continues to be sepsis, as it was two years ago at the time of a previous report.

The authors stated that the caliber of an unstretched urethra is equal to that of a no. 25 French catheter and the caliber of a slightly stretched urethra is equal to that of a no. 26 French catheter. Up to the present, most resectionists have been using a no. 28 French catheter for a fairly long period, jamming the mucous membrane and crowding out the local blood supply by pressure, thus heating the membrane, which, having temporarily lost its blood supply by pressure, has also lost its resistance and has a tendency to become "cooked" or "toasted." To prevent this, Plaggemeyer and Weltman use the no. 28 French catheter rapidly and for a minimum amount of time, working fast and getting out a maximum of tissue; they then shift to the no. 24 French catheter and trim the edges, if necessary, and make a final inspection for bleeders. This procedure tends to insure the maximum of success with a minimum of surgical trauma. They resect the vas deferens as a routine procedure and report that they have never had epididymitis develop following this procedure, although occasionally funiculitis occurs, which readily subsides. The large bilateral lobe, extravescical type of adenoma, with no middle lobe, is the most difficult to resect. This type must be excavated (shelled out), keeping distal to the neck of the bladder lest it be cut away and result in extravasation of urine. At least three quarters of the gland must be removed to secure results. The enormous middle lobe causes trouble at times, until enough is cut away to see the landmarks clearly.

Plaggemeyer and Weltman offer the following factors as probable contraindications to resection: (1) large extravescical prostates; (2) large intravesical prostates extending backward under the trigon in an embarrassing proximity to the ureteral orifice; (3) deeply embedded prostatic calculi; (4) large vesical calculi, with foully infected bladder; (5) dependent diverticula of the bladder, and (6) patients in their early fifties, with a mild diffuse infection and possible beginning adenoma. The infection should be treated first; otherwise, having carried out a resection, the operator may find himself with an unpleasant responsibility for eradicating the infection, a matter of two years of work.

the procedure used in this case was similar to that advocated by Bigelow a number of years ago for the performance of litholapaxy. It seems likely that this procedure would greatly facilitate the performance of prostatic resection when, for any reason, it is not feasible or it is difficult to pass instruments of large caliber through the anterior portion of the urethra.

Boyd<sup>41</sup> reported 2 cases of urethral injury from the use of the metal covered bakelite sheath in transurethral prostatic resection. One patient complained of a most unusual, frequently recurring burning in his rectum after operation which continued intermittently for four weeks; the urine remained cloudy, especially the first glass; there was a little loss of control of the urine when the irritation of the neck of the bladder was most annoying. At the end of the fourth week examination with the panendoscope revealed rather extensive but seemingly superficial injury of the floor and of the lower part of the lateral walls of the membranous portion of the urethra. In another patient (spinal anesthesia) the right leg jerked into extension twice during the operation, and three weeks after operation the panendoscope showed definite injury of the lower right side of the membranous portion of the urethra, mucus being adherent along the lower right side of the whole length of this portion.

During these two operations each of the telescopes used was so badly damaged by the current jumping from the loop to a point near the lens that it had to be repaired before it could be used again. Both of them were found to have a hole through the metal.

Walker<sup>42</sup> stated that there are two chief danger points in carrying out prostatic resection: the region of the trigon and the posterior portion of the urethra. An injudicious cut in the trigon will open up the space of Denonvillier, and a cut in the posterior portion of the urethra will perforate the rectum. Of these two disasters, the former should be feared more. Two of Walker's patients have passed urine by rectum a few days after resection without being any the worse for their temporary fistula. Over 20 suffered from severe sepsis following resection, and, although he has no definite proof for this, Walker expressed the belief that in some of these cases of protracted sepsis the space of Denonvillier had been infected. In order to prevent this, when tissue is removed at the level of the sphincter the instrument should be kept horizontal and not dipped down into the bladder.

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41. Boyd, M. L.: Urethral Injury from Using the Metal Covered Bakelite Sheath in Transurethral Prostatic Resection, *J. Urol.* **38**:100-101 (July) 1937.

42. Walker, K. M.: Transurethral Resection of the Prostate: A Review of Fourteen Years' Work, *Brit. M. J.* **1**:901-903 (May 1) 1937.

cedures with the amount lost during prostatic resection. He found that the amount of blood lost during prostatic resection compared favorably with that lost during other surgical procedures of equal magnitude. The method for determining the amount of blood lost at the time of operation seems accurate and should be of value in determining the amount of blood lost under any similar circumstances. It appears that the amount of blood lost during prostatic resection is less than the amount lost when suprapubic prostatectomy is performed.

*(To Be Continued)*

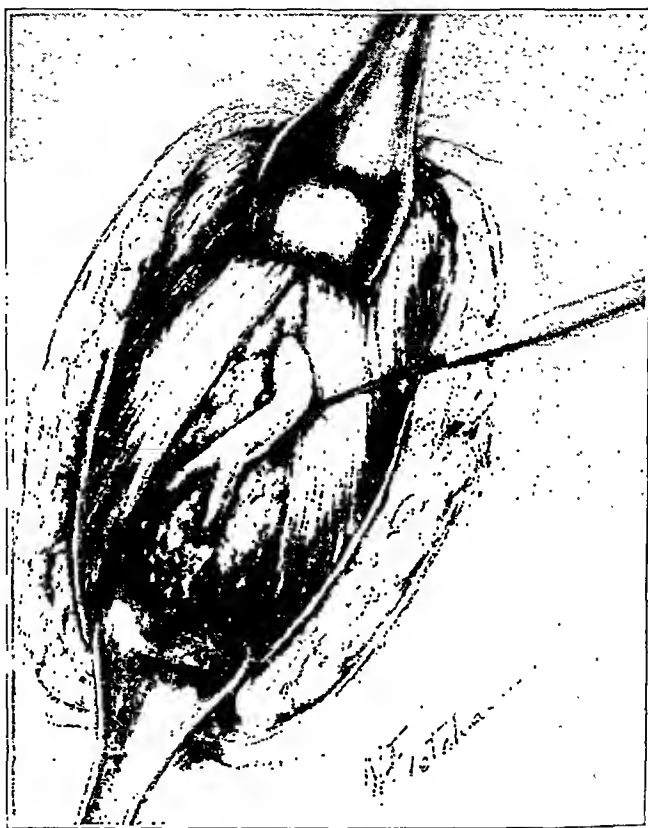
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### CORRECTION

In the article by Drs. Gray and Heifetz entitled "Lymphoid Hyperplasia of the Appendix, with a Note on Its Role in Acute Appendicitis," in the November issue (ARCH. SURG. 35:887, 1937), "fourteen thousand appendixes" in the second line of the first paragraph on page 900 should read "fourteen hundred."

dorsally. The skin of the back is clipped, shaved and sterilized with the usual iodine-alcohol technic. Sterile towels are applied to isolate the operative fields.

On the right side, the incision in the skin, 4 cm. long, is started about 2 cm. from the midline, running parallel to and along the lower border of the twelfth rib. This incision is carried down through the skin and subcutaneous tissue, and the lumbodorsal fascia is well exposed. This fascia is then incised throughout the length of the incision. At



The right renal artery and its bifurcation are shown. The artery is held forward at the point where the Goldblatt clamp is to be applied.

about the lower third of the incision the union of the fasciae of the internal and that of the external oblique muscle can be identified. The fascia of the internal oblique muscle must be incised, as its course inward and downward is followed. By blunt dissection the bundle of the thick longissimus dorsi muscle can be partially freed from its surrounding structures and retracted medially as a whole. This procedure leaves the tendinous origin of the transverse abdominal muscle exposed. This muscle forms the floor of the incision and the roof of the perirenal

# EFFECT OF PASSING RENAL BLOOD THROUGH LIVER IN DOGS WITH EXPERIMENTAL HYPERTENSION

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For many years it has been recognized that the liver has as one of its functions a detoxifying action. It excretes certain heavy metals, dysentery toxin and ricin into the bile.<sup>1</sup> It has been shown that the injection of phenol, benzoic acid and phenoltetrachlorophthalein in amounts which normally produce no reaction may prove fatal in hepatectomized dogs.<sup>1</sup> It is known that in the absence of the liver amino acids injected into an animal are not destroyed.<sup>2</sup> Numerous observers have suggested that the liver protects the body from both endogenous and exogenous poisons. The liver takes up the bulk of chemical poisons, removes chloroform and phenol from the organism and protects it against the alkaloids. Most of these actions of the liver are based on the so-called glycuronic acid synthesis, whereby glycogen unites with these substances to form corresponding acids which are removed by the kidney. Many times the lethal dose of certain micro-organisms can be injected into the portal vein.<sup>3</sup>

As initially described by Goldblatt,<sup>4</sup> partial constriction of the renal artery, which produces ischemia in the kidney, results in a permanent hypertension in dogs<sup>4</sup> and monkeys.<sup>5</sup> There is the possibility that a substance is formed in the damaged kidney and carried in the blood stream that is responsible for the elevated blood pressure. As yet no such substance has been demonstrated in the blood stream either by

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Supported by a grant from the John and Mary R. Markle Foundation.

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1. Wright, Samson: *Applied Physiology*, ed. 6, New York, Oxford University Press, 1936, p. 490.

2. Wright,<sup>1</sup> p. 489.

3. Rolleston, H., and McNee, J. W.: *Diseases of the Liver, Gallbladder and Bile Ducts*, ed. 3, New York, The Macmillan Company, 1929, p. 18.

4. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: *J. Exper. Med.* **59**:347, 1934.

5. Goldblatt, H.: *Am. J. Path.* **12**:760, 1936.



promptly from the anesthesia and seemed to be little disturbed by the procedure. The wound healed by first intention. For the following ten days the readings of the dog's blood pressure were 120, 120, 135, 140, 160, 160, 140, 170 and 140 mm. of mercury.

On November 21, Goldblatt clamps were applied to both renal arteries, and a degree of constriction was produced to occlude approximately 75 per cent of the normal flow of blood. The animal seemed little disturbed by the procedure; it recovered promptly from the anesthesia. Both wounds healed by first intention. During the next four weeks the blood pressure rose slowly but steadily and reached a level between 200 and 220 mm. of mercury. It has remained at this elevated level for ten weeks, and the animal is alive and well with a definite and persistent hypertension at the time of writing, March 15, 1937.

EXPERIMENT 2.—(a) *Reverse Eck fistula*, (b) *carotid loop* and (c) *application of Goldblatt clamps to the renal arteries*.

On Oct. 24, 1936, with the animal under anesthesia induced by intravenous injection of pentobarbital sodium, the inferior vena cava and portal veins were exposed in a healthy male dog, which weighed 28 pounds (12.7 Kg.), and an anastomosis was made between the two vessels. The vena cava was ligated just cephalad to the fistula. The animal withstood this procedure well and recovered promptly from the anesthesia. The wound healed by first intention. The postoperative course was uneventful save that for several days after the operation the animal exhibited moderate edema of the penis, scrotum and lower extremities. This edema disappeared within a few days.

On November 6, a van Leersum carotid loop was made in the animal's neck while it was under pentobarbital sodium anesthesia. The wounds healed slowly because of a marked secondary infection, but by the seventeenth postoperative day satisfactory determinations of blood pressure could be made. These determinations were made daily from November 23 to December 13 and showed a level of approximately 150 to 160 mm. of mercury.

On December 14, with the dog under pentobarbital sodium anesthesia, Goldblatt clamps were applied to the renal arteries. The recovery was uneventful, and both wounds healed by first intention. The blood pressure rose sharply to a level of 200 mm. of mercury within a week. By the fourth postoperative week the blood pressure had risen to a level of from 220 to 240 mm. of mercury. This level of pressure was maintained for more than six weeks. At the time of writing, March 15, 1937, the animal is alive and well, with a blood pressure of 230 to 240 mm. of mercury.

EXPERIMENT 3.—(a) *Carotid loop*, (b) *application of Goldblatt clamps to the renal arteries* and (c) *reverse Eck fistula*.

On Sept. 10, 1936, with the animal under anesthesia induced by intravenous injection of pentobarbital sodium a van Leersum carotid loop was made in the neck of a healthy young male dog which weighed 17½ pounds (7.9 Kg.). The wounds healed slowly because of secondary infection, and it was not until the eleventh postoperative day that determinations of blood pressure could be started. In order to establish a normal level, twenty-five readings were taken over a period of one month.

On October 23, Goldblatt clamps were applied to the renal arteries with the dog under pentobarbital sodium anesthesia. Within three days the blood pressure had risen to 190, but in the course of the next ten weeks it fell to approximately 160 to 170 mm. of mercury. This was not considered to be a satisfactory level of hypertension for experimental purposes; so the clamps were reexplored on Jan. 5, 1937,

was shunted through the liver. In all four experiments the findings were essentially the same. In experiment 4 the urea nitrogen content of the blood was studied and was found to be slightly elevated for several days after operation. No explanation can be given for this, unless the renal function temporarily was impaired by back venous pressure. The experiments described indicate that the passage of the venous blood of the kidneys directly through the liver does not prevent the production of experimental hypertension in dogs, nor does it affect hypertension which has already been produced.

minute abrasions there is sufficient exudation of lymph to provide an ideal culture medium in which the various bacteria present on the skin can grow luxuriantly. This in turn results in sufficient edema to cause actual pressure necrosis of the loop early in the postoperative course. On the other hand, it is not felt that the minute stubble left by clippers hinders sterilization of the skin by the usual benzine, ether-iodine-alcohol technic.

The animal is next transferred and securely strapped to the operating table. Two folded towels placed beneath the neck are adequate to aid in exposure and will not place too great a tension on the artery during the course of its isolation. The skin of the operative field is scrubbed with soft soap after it has been freed of fat with benzine; it is then washed with alcohol and ether. The skin is painted once with 7 per cent tincture of iodine, which is allowed to oxidize and then is removed with alcohol. A field large enough to permit the incision shown in the illustration is draped with sterile towels, and the rest of the animal is covered with the usual laparotomy sheet.

Emphasis should be placed on the careful planning of the incisions in the skin that are to form the loop. The midportion of the flap must lie directly over the carotid artery. By palpation the course of the artery is outlined along the tracheal border. With this course as the midline of the proposed flap, about 2 cm. of skin is taken on each side, this marking the width of the flap. The medial incision is then made slightly above the thyroid cartilage and is extended caudad to a point about 1 cm. lateral and 1 cm. above the manubrium sterni. In running parallel to the artery, the course of this incision is slightly diagonal across the trachea. The lateral incision again lies about 2 cm. from the line of the carotid artery and parallel to it. Instead, however, of being equal in length to the medial incision, the lateral incision is only half as long and lies opposite the midhalf of the former, as shown in the illustration. It has been customary to make this lateral incision equal in length to the midline incision. There is no need for this extra length, however, and it is a great hazard to the successful healing of the loop because it materially decreases the blood supply of the cutaneous flap. Also, in the final suturing of the artery within the flap the shorter incision leaves a junction of three free edges rather than four.

After the incisions are outlined, they are carried down through the skin to the subcutaneous tissues over the platysma myoides muscle. It is in the plane between the skin and that muscle that the flap is undermined. Though this procedure may seem to leave the skin without adequate blood supply, necrosis has never been observed. On the other hand, a flap so cut bears no tissue which may become edematous and cause subsequent necrosis owing to intrinsic pressure. With the blade of the knife held at an oblique angle, the skin is under-

their course. At this point the artery may be included in the skin and temporarily held there by two short lengths of hernia tape, as shown in the sixth section of the illustration. This procedure readily permits placing the row of on end mattress sutures which are to hold the cutaneous edges of the neck. As this line is always subjected to a fair degree of tension, the use of on end mattress sutures is considered important, for it is the only suture which not only will act as a tension suture but will permit accurate approximation of the edges of skin. This suture also serves to bring the platysmal muscle and the subcutaneous tissues close together. In order to insure the evenness of this portion of the closure, it has been found advantageous to place this entire row of sutures before attempting to tie any of them. It is the midhalf of the medial incision which, of course, is approximated to the lateral. After their placement, the sutures are drawn taut and tied. They should be tight enough to secure adequate approximation of the edges of skin, but not tight enough to cause strangulation of the tissue.

The cutaneous flap will then be found to evert of its own accord toward the lateral aspect of the neck. The artery can easily be made to lie in the midportion of the flap. It is at this point that the most important suture in the entire procedure is placed. With the artery lying deep in the flap, a continuous suture of fine silk is started at the place where the vessel emerges from the muscle borders. The suture is so placed as to include the artery in a sling of skin which starts well above the junction of the three lines of suture and which will isolate the vessel from the line of suture of the under-side of the completed loop. These steps are well shown in the illustration. The importance of placing the artery deep within its flap rests on the following observation. About four days after operation, the cutaneous suture lines become infected. When the artery is allowed to rest directly on the line of cutaneous closure of the under-side of the loop, this inflammatory process spreads rapidly to the wall of the artery, weakening it sufficiently to allow erosion and subsequent fatal hemorrhage. When, however, the artery is protected by an intervening line of subcuticular tissue, hemorrhage has never been observed.

The last steps are relatively simple. As shown in the illustration, the proximal and distal quarters of the flap are closed with Staige-Davis sutures of medium silk, while the skin tube is closed with a continuous suture of the same material. This suture is started and finished as a purse-string, uniting all four edges of skin at their points of junction. This suture is placed intracutaneously.

The type of dressing is of importance. One thickness of gauze is placed beneath the loop. Along each border is placed a strip of gauze 4 by 4 inches (10 by 10 cm.), rolled in such a fashion as to relieve

# ARTHROPLASTY OF THE HIP

## A STATISTICAL STUDY OF SIXTY OPERATIONS

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There was used for this study a series of fifty-seven patients on whom arthroplasty of the hip was performed for various causes; three of the patients underwent bilateral arthroplasty, making a total of sixty operations. Included in the study were the age range, the types and variations of operative technic, the range of motion, the time elapsed since operation, the persistence of pain, the type of mobilization and the patient's personal reaction to the value of the operation regarding motion, pain and ability to get around and carry on his work.

Questionnaires were sent to all of these patients, and from these their personal reactions were obtained. From a clinical standpoint, several of the results which were classified as fair would have been classified as poor had not the personal reaction of the patient been taken into consideration.

### RESULTS OF STUDY

To classify the results, the following criteria were used. The operation was considered a failure when the patient had considerable pain or when complete, or almost complete, ankylosis resulted. The results were classified as good when there was at least 45 degrees of flexion and no pain and the patient was able to walk at least one-half mile (804 meters) without pain. The results were classified as fair when there was less than 45 degrees but more than 20 degrees of motion and the patient had little or no pain and was personally well satisfied with the result, either because of decreased pain, increased motion or better position of the limb. Several patients expressed satisfaction in spite of ankylosis because of decreased pain and betterment of position. In such cases the operation has been considered a failure.

It was noted, especially in the cases of hypertrophic arthritis, that pain was almost constantly present for from twelve to fourteen months. After this time the pain decreased markedly, and in some of the cases in which the results appeared to be fair or poor because of pain the actual end-results were good.

The classification of results according to the condition for which arthroplasty was done is found in table 1. It will be noted that there

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obtained on the side on which the first operation was done, but rapid ankylosis occurred on the other side. This case was one of atrophic arthritis. In the third case only fair results were obtained on each side. The patient could get around the house without much distress, but considerable pain and tiredness resulted from going out of the house a few steps.

In one patient who was operated on following suppurative arthritis ankylosis developed which was resistant to two manipulations, and a second arthroplasty was done. On reoperation it was thought that the acetabulum had been made too deep, and the rim was cut down. There was much interposed scar tissue where the fascia had been placed. After the second arthroplasty, suppuration occurred, but despite this a splendid result was obtained, with no pain and with good range of motion. In fact, the boy won the high school single tennis championship last season.

TABLE 2.—*Results of Arthroplasty Classified According to Age Groups*

Age at the Time of Operation	No. of Operations	Good Results		Fair Results		Failure	
		No. of Cases	Per-centage	No. of Cases	Per-centage	No. of Cases	Per-centage
0-18.....	4	0	0.00	3	75.00	1	25.00
14-20.....	12	5	41.66	3	25.00	4	33.33
21-30.....	20	10	50.00	6	30.00	4	20.00
31-40.....	7	1	14.28	1	14.28	5	71.42
41-50.....	10	2	20.00	5	50.00	3	30.00
51-60.....	7	3	42.85	3	42.85	1	14.28
Total cases.....	60	21	35.00	21	35.00	15	30.00

Nevertheless, the operative result has been listed as a failure because the boy had a persistently draining sinus, owing to which he was unable to go swimming. The first arthroplasty, which resulted in ankylosis, was done while he was only 15 and possibly before the metaphysis had closed.

With the possibility in mind of epiphysial activity affecting the end-results, the results were classified according to ages in table 2.

The head of the femur fuses about the fifteenth or sixteenth year, and in the four cases in which arthroplasty was done before this time not a single good result was obtained. The next group in which poor results were obtained was made up of patients from 30 to 50 years of age. This included most of the patients operated on for atrophic arthritis, so the average was lowered more probably by this than by any age difficulty.

Most of the patients with suppurative arthritis were operated on between 21 and 30 years of age. As good results followed operations performed for this causative agent, a high percentage of good results would be expected in this age group. This was found to be the case.

In fifty-two cases a single layer of fascia lata was placed over the newly constructed head and anchored by sutures through a drill hole. This gave the higher percentage of good results, namely, 38.46 per cent. In only one case was a double layer of fascia used, that is, one layer over the acetabulum and the other over the newly constructed head. Whereas one case is not enough on which to form an opinion, there may be a greater tendency for the formation of scar tissue following this method, as rapid ankylosis occurred in this case. If all cases in

TABLE 5.—*Analysis of Failures*

Basis of Arthroplasty	Failures, No. of Cases	Pain, No. of Cases	Limited Motion, No. of Cases	Limited Motion and Pain, No. of Cases	Persistent Sinuses, No. of Cases
Hypertrophic arthritis.....	2	1	0	1	0
Atrophic arthritis.....	9	0	8	1	0
Suppurative arthritis.....	2	0	1	0	1
Gonorrheal arthritis.....	1	0	1	0	0
Slipped epiphysis.....	1	1	0	0	0
Congenital dislocation.....	3	0	2	1	0
Osteomyelitis.....	0	0	0	0	0
Aseptic necrosis.....	0	0	0	0	0
Totals.....	18	2	12	3	1
Percentage.....	100%	11.0%	66.0%	16.5%	5.5%

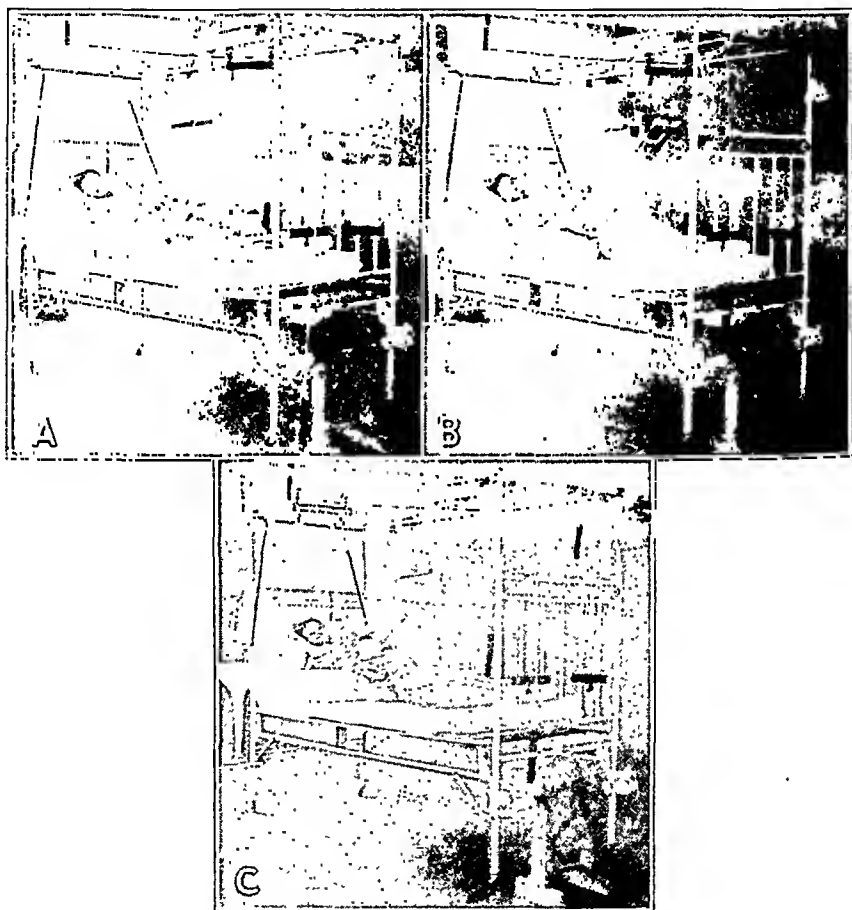
TABLE 6.—*Analysis of Fair Results*

Basis of Arthroplasty	Fair Results, No. of Cases	Slight Pain, No. of Cases	Limited Motion, No. of Cases	Limited Motion and Pain, No. of Cases	Persistent Sinuses, No. of Cases
Hypertrophic arthritis.....	6	1	2	3	0
Atrophic arthritis.....	8	6	0	2	0
Suppurative arthritis.....	3	1	2	0	0
Gonorrheal arthritis.....	0	0	0	0	0
Slipped epiphysis.....	2	0	2	0	0
Congenital dislocation.....	0	0	0	0	0
Osteomyelitis.....	2	1	1	0	0
Aseptic necrosis.....	0	0	0	0	0
Totals.....	21	9	7	5	0
Percentage.....	100%	42.84%	33.32%	23.80%	

which fascia was used are considered in one group, as in table 4, good results were obtained in 37.73 per cent. The results in the few cases in which muscle and fat were used are not conclusive, although in those in which fat was employed there was not a single good result. The failures are not due to variations in operative technic.

In comparing tables 5 and 6, it will be noted that 42.84 per cent of the results were listed as fair because of slight pain, whereas 66 per cent of the failures were so classed because of ankylosis. There was a greater tendency to ankylosis in the atrophic type of arthritis. Pain was the predominating cause of fair results in cases of atrophic arthritis,

frame was used, as shown in the accompanying illustration. This consists of a frame, with a track overhead, so balanced that both active and passive abduction, flexion, internal rotation and traction can be obtained while the patient is in bed. This is used after the period of immobilization. Of those cases in which this apparatus was used good results were obtained in two and fair results in three, while two cases ended in fail-



Patterson's abduction frame. *A* shows the hip in extension but in a neutral position. In *B*, the extension is released while the patient passively or actively flexes the leg. In *C*, the extension is released while the leg is abducted. Note the hanger is at the extreme outer limit of the track.

ure. In one, failure was due to pneumonia, which developed after the patient was discharged from the hospital two months after operation. This necessitated a prolonged period without mobilization. In the second case, one of hypertrophic arthritis, suppuration occurred, and a sinus had to be resected twice. This prolonged the period of immobilization.



# HYGROMA COLLI CYSTICUM AND HYGROMA AXILLARE

PATHOLOGIC AND CLINICAL STUDY AND REPORT OF TWELVE CASES

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BROOKLYN

Hygroma, derived from the Greek *hygros* (moist) and *oma* (tumor), is a term which has often been used loosely to include various types of cysts containing a thin watery fluid. The designation cavernous lymphangioma has frequently been applied to the cystic form of this tumor. In a stricter sense, hygroma should be limited to multilocular cystic tumors of benign neoplastic nature which have a lymphatic origin and whose cavities are lined with true endothelium. These tumors originate, for the most part, in the neck and axilla and are then designated as hygroma colli cysticum and hygroma axillare. Occasional cases of hygroma occurring in the groin or in the retroperitoneal space have been reported.

Since these cystic tumors are relatively rare, the descriptions in the literature are limited in many instances to case reports, which are often incomplete, contradictory and unsupported by records of careful pathologic examination. The manner of growth and propagation of hygroma, its potentiality of increasing in size to an almost unlimited extent and its tendency to penetrate and destroy anatomic structures have heretofore been little understood. Because of the relatively obscure nature and the clinical importance of hygroma, this tumor deserved a careful and critical study to establish its pathologic nature and its manner of growth.

Opportunity was afforded to make gross and microscopic examinations in 12 cases of hygroma. As a result of these studies it has been possible to demonstrate the manner of growth and propagation of hygomatous cysts and thus to make clear this baffling problem. In addition to an account of the pathologic nature of hygroma, this report includes a critical clinical analysis of 12 cases of hygroma observed between 1925 and 1933 in the surgical departments of the Long Island College Hospital and the Long Island College of Medicine. Of the 12 hygromas studied, 10 occurred in the neck and 2 in the axilla. They comprised 1.2 per cent of the 981 tumors of all kinds, benign and

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of the tumor were small, the term hygroma was applied; if they were large, hydrocele was used. Thus the terms hydrocele colli and hydrocele capitis arose in the classification of tumors which were in many instances probably true hygromas. Virchow objected to these terms, because he doubted that the fluid in these tumors occurred in preexisting true anatomic sacs. He considered "hydrocele colli" an obscure formation in which the sacs were newly formed and contained an encapsulated fluid which was probably a transudate.

Arnold<sup>8</sup> reported 2 cases of hygroma colli cysticum and convinced himself that the growths did not arise from the intercarotid ganglion since the cystic cavities were lined with endothelium. In his second case, he described atrophic muscle fibers coursing through the cystic tumors. His conception of the growth of the tumors was that the cellular elements of true connective tissue disintegrate, forming round cystic spaces in which fluid accumulates secondarily.

Koester<sup>9</sup> made one of the first important contributions to the subject. By means of silver solutions, he demonstrated an endothelial lining in the cysts of a cervical hygroma. He concluded that the cystic cavities of hygroma arise by a widening of preexisting lymph vessels and that this accounts for the penetration of the tumors into surrounding organs and tissues. He designated the hygromatous tumors as "lymphangiectasia congenita." Borst<sup>10</sup> studied lymphangioma located within a lipoma and offered evidence of the formation of new lymph capillaries from the intercellular canalization of buds which sprouted from the endothelial lining of the dilated lymph vessels and penetrated the adjacent connective tissue. However, he did not observe this phenomenon in hygroma and therefore was unable to say whether hygroma develops merely from preexisting lymph spaces or by the actual growth and propagation of newly formed lymphatics. Accordingly, the etiology and manner of growth of hygroma remained obscure.

Langemak<sup>11</sup> discussed the possible development of hygroma from subcutaneous bursae not connected with the joints. Opokin<sup>12</sup> felt that the new cysts of the growing hygroma arise from developmental changes

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8. Arnold, J.: Zwei Fälle von Hygroma colli cysticum congenitum und deren fragliche Beziehung zu dem Ganglion intercaroticum, Virchows Arch. f. path. Anat. **33**:209, 1865.

9. Koester, K.: Ueber Hygroma cysticum colli congenitum, Verhandl. d. phys.-med. Gesellsch. in Würzb. **3**:44, 1872.

10. Borst, M.: Die Lehre von den Geschwülsten, Wiesbaden, J. F. Bergmann, 1902, vol. 1, pp. 191-204.

11. Langemak, O.: Die Entstehung der Hygrome, Arch. f. klin. Chir. **70**:466, 1903.

12. Opokin, A.: Zur Lehre über die Patho- und Histogenese des Lymphangioms (Ein Fall von kavernösem Lymphangiom der Halsgegend beim Erwachsenen.), Frankfurt. Ztschr. f. Path. **9**:143, 1911.

angioma. They agreed with Dowd as to the probable origin of hygroma from lymphatic rests derived from the jugular sacs. They observed microscopically that the walls were made up of inactive lymphatics, and the lining endothelium of the cyst itself contained few cells in the process of division. Therefore, they concluded that the extension of hygroma into the axilla and the mediastinum is not due to an invasive power on the part of the endothelium. According to this view it actually originates in anlagen occupying these regions but lies quiescent until cyst formation causes it to appear as a visible swelling. Vaughn<sup>21</sup> reported a case of cystic hygroma of the neck and in considering the etiology agreed with Thompson and Keiller as to the origin of cystic hygroma. These views were accepted likewise by MacGuire,<sup>22</sup> who reported the history and the pathologic observations in a case of hygroma and referred to 7 others. He advised against radical operative procedure when roentgenograms show mediastinal extension of the tumor.

Dowd and Ribbert suggested that hygroma colli cysticum is derived from lymphatic rests which are remnants of the primitive jugular sacs and which possess an independent power of irregular growth and penetration. This view has in recent years been rather generally accepted, although support for it has heretofore not been offered. I believe that the pathologic studies subsequently to be reported provide histologic evidence of the specific conditions characterizing the origin and development of cystic hygroma. By presenting this evidence I hope to clarify the obscure nature of this tumor.

#### ANALYSIS OF CASES OF HYGROMA

*Etiology.*—According to the most plausible theory, hygroma arises from sequestrations of lymphatic tissue, derived in the case of cervical hygroma from the jugular sac, which retain their independent power of irregular growth. Comparative anatomic studies of the development of the lymphatic system were made by McClure and Silvester.<sup>14</sup> In figure 1 is shown the relation of the left jugular lymph sac of an 11 mm. cat embryo to the internal jugular and subclavian veins before the jugular and subclavian approaches have joined with the venous system. Figure 2 illustrates the structure of the lymphatics and their ultimate communications with the veins in the pig-tailed macaque.

In order to elucidate this theory, it may be well to review briefly the knowledge of the early development of the lymphatic system. Sabin<sup>23</sup>

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21. Vaughn, A. M.: Cystic Hygroma of the Neck: Report of Case and Review of Literature, *Am. J. Dis. Child.* **48**:149 (July) 1934.

22. MacGuire, D. P.: Cystic Hygroma of the Neck, *Arch. Surg.* **31**:301 (Aug.) 1935.

23. Sabin, F., in Keibel, F., and Mall, F. P.: *Manual of Human Embryology*, Philadelphia, J. B. Lippincott Co., 1912, vol. 2, pp. 709-716.

presented a new conception of the general structure and development of the lymphatic system in the fetus. In the primary stage of development a capillary plexus is formed from the jugular vein on each side. In certain areas along this vein, a part of the capillary plexus is cut off from the parent vein. This group of isolated spaces lined by endothelium remains for a short time, constituting the anlage of the lymphatic system. These isolated capillaries dilate and coalesce to form symmetrical lined sacs. In this manner the two primitive jugular sacs, one on each side, are formed. The thoracic duct connects the pelvic and retroperitoneal sacs with the left jugular sac and then forms an opening into the veins at the jugular valve. On the right there is a somewhat similar development.

The secondary stage of development involves the peripheral growth of the lymphatic vessels. Sabin has shown that this is accomplished by endothelial sprouts, which are derived from the lining of the jugular sacs and which penetrate the surrounding tissue and radiate outward over the body. In addition, there is the element of secretion from the endothelium of the newly formed lymphatics. This is the normal course of development of the lymphatic system. Through some anomaly of growth, fibrosis or other accident the primitive jugular sac (fig. 1) or portions of it may fail to establish a communication with the venous system. The lymphatic tissue thus sequestered may retain the power of growth inherent in the process of endothelial sprouting and penetration characteristic of the development of the normal lymphatic system (Sabin<sup>23</sup>). These are the two factors necessary for an explanation of the origin and growth of cervical hygromas.

The explanation of the origin of the sequestered lymphatic tissue still lies in the realm of assumption. However, the origin and growth of hygroma from these sequestrations, which have retained the power of growth just described, need hardly be assumed any longer in view of the studies here reported. It will be histologically demonstrated that hygromatous cysts arise primarily by the formation of fibrillar membranous sprouts derived from the lining walls of the cystic spaces. By the penetration into surrounding tissues and subsequent canalization of these sprouts, cysts are formed and propagate themselves in a manner somewhat analogous to the development of the early lymphatic system.

Predisposing or exciting causes are not known. Wassermann and Kahn tests were done in a number of instances on both the patient and the patient's parents and were uniformly negative. Tuberculous ancestry was present in 1 instance (case 4), and trauma seemed to be an activating cause in another case (case 1).

*Symptomatology.*—In the majority of cases of less advanced involvement the symptoms of hygroma were negligible except for worry

tion, as in case 4. There was rapid growth of the tumor, with associated glandular enlargements in the right cervical region due to infection with the streptococcus (case 9). In some ways it resembled the development of a malignant growth. There were no symptoms of general systemic character in any of the 12 cases except that in case 2 there was some mental dulness, which might have been due to markedly hypertrophic tonsils and adenoids. Very young children with hygroma, however, often are below par and suffer from anemia. In general, there were few direct or secondary complications, as indicated in 8 of the 12 cases. The tumors were rarely painful or tender. A recurrent tumor may cause symptoms notwithstanding that the primary growth may not have produced any. In case 10, for example, the floor of the mouth became involved after the removal of a hygroma in the upper anterior cervical triangle.

*Gross Pathologic Picture.*—The characteristic appearance of the tumor which has been surgically removed is that of a multilobular, multilocular cystic mass, in which the individual cysts vary from the size of a pinhead to that of a lemon. The walls of the younger cysts are extremely thin, delicate, friable and practically transparent; the walls of the older cysts are often thick and fibrotic (fig. 7). There is frequently generalized fibrosis in the older portions of the tumor, and consequently fragments of adjacent muscles, fascia, nerves and blood vessels are adherent to the excised mass.

In certain areas the mass is often spongy, giving the appearance of the ordinary rubber bath-sponge (figs. 42 and 45); in other areas there are large whitish zones of fibrosis. The cysts themselves are usually soft and fluctuant but rarely tense. The fluid within the cysts is serous, watery, clear or straw colored and occasionally turbid or blood stained. Not uncommonly the mass is intimately associated with groups of enlarged lymph glands, which are hyperplastic (figs. 11 and 12), at times edematous and occasionally fibrotic. These glands are encountered in the walls of the tumor and are thus doubtless directly involved in the pathologic process. The cystic spaces within the tumor are found to be lined by a thin, pearly white, glistening almost transparent membrane which resembles peritoneum or pleura. The cavities, together with their many recesses, septums and trabeculae, are lined in a similar manner. The trabeculae are often seen as isolated cords traversing the cystic cavities (fig. 14 *A* and *B*). Any remnants of muscle which are attached to the outer margins of the tumor often show separation and atrophy of the individual bundles, produced by the interposition of hygromatous tissue and cysts (figs. 14 *A*, VI and VII, 18 *A*, 30 and 31).

*Microscopic Pathologic Picture.*—Sections varying in thickness from 6 to 8 microns were cut from blocks of tumor tissue fixed in solution

Opokin<sup>12</sup> attributed the potentiality of forming new cysts and of metamorphosis into true endothelium. No evidence of such changes was observed in these studies.

It appears from the large number of transitional cells that hygromatous tissue itself is capable of producing an abundance of lymphoid tissue, germinating lymph follicles and possibly even lymph glands. Thus accumulations of lymphoid cells, both in the form of follicles and of large, dense zones (figs. 38 and 39), are produced from the endothelium in the cyst wall and do not represent infiltrations.

**Lymph Glands:** Groups of enlarged hyperplastic lymph glands are generally intimately associated with the hygromatous tumors. An illustrative example of such a gland is shown in figures 11 and 12. The lymph follicles are increased in number, and the germinating centers contain numerous lymphoblastic cells of various sizes and shapes, together with epithelioid cells and those of endothelial type. There is a striking frequency of karyokinetic figures in the germinating centers. The hilus of the hyperplastic lymph gland contains many large lymph sinuses, which are commonly entirely filled with lymphoblastic, lymphoid and epithelioid cells. Large blood spaces also are common.

**Trabeculae:** Densely fibrotic isolated and free trabeculae (fig. 14 A, III) are occasionally seen coursing through the cystic cavities of hygroma. Cross sections of such trabeculae (fig. 8) show that they are lined by endothelium similar to that of the cystic cavity. They reveal, moreover, that the trabeculae represent the persistence of arteries, which remain after the cyst walls in which they formerly ran have atrophied and disappeared. Thus the centers of the trabeculae show hyalinization of organized clots following thrombosis (fig. 8), and the peripheral zones show concentric hyalinization of the walls of the old artery. (The fibrosed vessels thus remain as isolated cords or trabeculae traversing cystic cavities in a fashion similar to the coursing of vessels through an old tuberculous or other abscess cavity.)

**Stroma at the Growing Margin of Hygroma:** The manner in which hygromatous cysts grow and propagate and their potentiality of destroying adjacent anatomic structures is made clear by a study of sections taken from the growing margin of a hygromatous tumor. In order to obtain and preserve conditions as much like those in living tissue as possible, the fresh tumor should be distended with an appropriate fixative, such as solution of formaldehyde, before its final immersion in the fixing fluid. If the cysts and their walls are allowed to collapse after the loss of their fluid, the microscopic characteristics peculiar to hygroma are largely destroyed, and histologic sections therefore fail to reveal them.

The histologic characteristics of the growing margin of a hygromatous tumor properly distended and fixed are well illustrated in the zone where the hygroma meets a normal anatomic tissue, such as a mass of

of the sprout in which the cyst is enclosed. New cysts are brought into being by this characteristic process of secretion within and subsequent canalization of the fibrillae composing a sprout. These minute young cysts are commonly in intimate association with the walls of the larger cysts (figs. 10 and 17).

**Circumscription and Isolation of Anatomic Structures:** As these fibrillar membranous sprouts penetrate adjacent tissues they characteristically circumscribe and isolate anatomic structures that lie in their paths, such as muscle fibers, nerves and blood vessels. Thereupon a cyst may form around such a structure. This formation is manifested in figures 9 and 10, in which the fibrillae are seen to enclose a nerve fiber at *N*. This gives rise to a perineural lymph space and then continues onward to form a small cyst. In this process of circumscription the nerve, muscle fiber or other structure receives an endothelial covering and is subsequently sequestered in the lymphatic or cystic fluid secreted by the fibrillae surrounding it.

Attention is directed to figures 9 and 10, in which a bundle of muscle fibers covered with endothelium is seen lying free and sequestered in a small cyst. The cyst in turn is lined by a layer of thin, flattened endothelial cells and subendothelial connective tissue and filled with a bluish (hematoxylin), foamlike coagulated lymph. The sequestered muscle fibers show vacuolar hydropic degeneration and fragmentation. The fibrillar stroma immediately surrounding the cyst is invading and destroying an area of muscle fibers, most of which show evidences of degeneration, fragmentation and approaching solution. Thus anatomic structures are circumscribed by the endothelial sprouts, and tissues are sequestered within the cysts formed by subsequent secretion between the fibrillae of the sprouts. This process is observed in many sections from the growing edge of hygroma.

**Death and Solution of Tissue Included in the Cysts:** A study of the sections reveals the ultimate fate of the normal tissues which have been engulfed in the cysts. Deep in masses of muscle, the cysts enclose fragments of muscle fibers (figs. 25 and 26). These fibers engulfed within the cysts show early evidences of atrophy and fatty degeneration, losing much of their affinity for stains. The striations, still apparent in some of the fibers cut longitudinally, indicate that their sequestration is a fairly recent event and that the cyst is young. As the cysts enlarge, pressure atrophy is noted in the tissues surrounding them.

In the cysts in which the process of sequestration is an older one, degeneration of the included tissue is more advanced. The muscle fibers in such an instance show extensive hydropic degeneration, disintegration and almost complete solution. Here and there faint striations are still apparent (figs. 23 and 24). Finally only isolated fragments of

engulfed, the fragments liquefy and disappear; thus a muscle fiber has been destroyed. This process is then repeated indefinitely.

**Connective Tissue:** Hygromatous stroma, composed of endothelial and connective tissue sprouts derived from the walls of the cysts, has been illustrated (figs. 17, 21 and 30). Further histologic investigation reveals that this infiltrating stroma is composed of bundles of fibers, arranged in parallel strands, and a reticular network. These fibrillar membranes on differentiation with Mallory's aniline blue method are seen to be comprised of blue-staining collagen fibrillae and deep orange or reddish fibers. They contain also a large number of fine elastic fibrillae demonstrable after the method of Verhoeff. The elastic tissue occurs in relative abundance in the stroma of the cyst walls. Van Gieson's stain for connective tissue imparts to the infiltrating fibrillar membranes a rich red stain, thus sharply differentiating them from the muscle (fig. 30).

**Fatty Degeneration of Muscle and Formation of Adipose Tissue:** As a result of the infiltration of the muscle with hygromatous stroma and the circumscription of individual muscle fibers, the latter undergo atrophy and fatty degeneration (fig. 31). Fat droplets, stainable by osmic acid and sudan III, accumulate within the muscle fibers before the contour and striations of these fibers indicate their loss of identity. These fat droplets increase in size and number and coalesce to form large globules of fat. The peripheral fibrillae of an individual fiber are often seen still enclosing the fat globules. Finally all the fibrillae disappear, and only the outlines of a fiber, replaced by fat globules, remain (fig. 32).

This replacement of muscle fibers by true adipose tissue is a characteristic process at this stage. The former muscle fibers, transformed into fat, coalesce to form large areas of adipose tissue (fig. 32), frequently seen in the walls of large cysts and adjacent regions. This adipose tissue is therefore the end result of the destructive action of hygroma on normal tissues.

**Nature of the Cystic Fluid.**—Unless infection (case 4) or hemorrhage (case 2) has occurred, the fluid characteristic of hygromatous cysts is thin, watery and clear or straw colored. It is practically free of albumin and globulin and does not coagulate on cooling. Storch<sup>5</sup> mentioned that in 2 cases which antedated his own observations there were respectively 4 per cent and 11 per cent of protein in the fluid. The method of determining the amount of protein was not given. Cholesterol crystals in large numbers are often seen floating on the surface of the fluid, particularly in cases in which hemorrhage with hemolysis has occurred. In the fluid from a typical, uncomplicated tumor, the sediment thrown down by centrifugation showed small numbers of lymphocytes.



tively. In the remaining 9 cases the tumor occurred on the right side. The areas involved were the right anterior cervical triangle and mediastinum once, the right cervical anterior triangle alone once, the right submandibular and posterior triangle once, the posterior triangle twice, the anterior midneck once, the right shoulder and arm once and the axilla twice. There was no case of bilateral involvement.

*Diagnosis.*—Errors in the diagnosis of hygroma before operation are frequent, and at times a correct diagnosis is well-nigh impossible. These presumptive diagnoses were made before hospitalization: hematoma, angioma, tuberculous adenitis, simple cyst, lipoma, bronchial cyst, goiter and benign lymphatic tumor. After the usual period of study in the hospital, the preoperative diagnosis was correct in 7 of the 12 cases. In the remaining 5, the tumor was thought to be a cyst originating in the lymphatic glands or the branchial cleft: a simple cyst in 1, a lipomatous tumor in 1 and a growth of undesignated type in the remaining 3. The diagnoses of lymphoblastoma, Hodgkin's disease and acute cervical adenitis with abscess had been suggested in the case of hygroma secondarily infected.

A positive clinical diagnosis can usually be made from the history and the results of physical examination. There is commonly a history of a soft, fluctuant, multilocular mass appearing at birth or in early childhood in the lateral cervical region or in the axilla and slowly increasing in size. As a rule the tumor is not tender or compressible. The overlying skin is not adherent, and its thinness may give the mass a bluish, translucent appearance. Accordingly, the tumor transilluminates well when a bright light is applied. Fluctuations in size are common, and there may be a history of temporary complete disappearance with subsequent reappearance. There may have been periods of infection during which the mass was inflamed, tender, tense and associated with toxemia. The tumors are diffuse in appearance, poorly circumscribed and inclined to involve neighboring structures in their growth. In various areas of the soft mass, irregular firm nodules, which may be trabeculae, areas of fibrosis or groups of lymph glands, are often palpable. The regional lymph glands are, as a rule, not enlarged.

*Differential Diagnosis.*—Since the preoperative diagnosis of hygroma appears difficult, the two principal conditions with which it may be confused should be mentioned, namely, cyst originating in the branchial cleft and lipoma. Cysts of the branchial cleft are likely to be single, rounded or oval, unilocular and smaller than hygroma. They are rather tense, firm and well circumscribed; often deep-seated, they occur principally in the anterior triangle. There is no associated atrophy of the overlying fat and skin. Furthermore, on gross and microscopic exami-

After this treatment, there was a rapid improvement in the child's condition and a satisfactory diminution was noted in the size of the mass (fig. 47 *A* and *B*).

*Clinical Course and Prognosis.*—A study of the reported cases and a limited personal experience led Storch<sup>5</sup> to report that, although hygroma was considered a benign tumor, the prognosis was poor. If no treatment was instituted the mass enlarged, sometimes slowly, sometimes rapidly. Death in children resulted from malnutrition. Storch stated further that if a hygroma became infected and if the child survived the infection cure was established. He cited a case of this kind in the experience of Wernher. Figi<sup>24</sup> had never seen a cure follow an infection. According to Boyd, hygroma is seldom met with after puberty, since previous infection results either in death or in spontaneous cure. The mass may involve important structures, such as the mediastinum, with consequent complications. Death, however, is most likely to occur as a result of infection and suppuration following simple incision and the institution of drainage. The tumor may become red and inflamed and be mistaken for an abscess. True suppuration or abscess formation is rare but may occasionally occur. When the hygroma becomes infected, the resulting sepsis is usually severe, as in a case in which there was secondary infection with the streptococcus (case 9). In no instance in this series was there a spontaneous rupture or even threatened rupture of the hygroma. It seems surprising that this accident had not occurred in several cases in which the skin overlying the tumor had become so thin as to be almost transparent.

*Treatment.*—Since the prognosis with palliative treatment is poor, early and radical surgical resection is the treatment of choice. Various forms of therapy have been tried but have proved ineffectual. Expectant treatment with the hope of spontaneous improvement is a dangerous procedure for two reasons. In the first place, a considerable risk is involved in the possibility of secondary infection in the hygroma following an intercurrent tonsillar or respiratory infection (case 9). Alarming sepsis and toxemia with a resultant fatal outcome may ensue, as in the series of cases reported by Figi,<sup>24</sup> in which a high mortality was due to intercurrent infection. In the second place, as a consequence of prolonged palliative treatment, the hygroma may reach such proportions or may extend so far into inaccessible areas, particularly the mediastinum, as to render surgical removal impossible. The extreme youth of the patients is often considered a contraindication to surgical treatment. Of these patients, 4 of whom were under 3 years of age, only 1, an infant of 6 months, died. This fatality was due to shock caused by

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24. Figi, F. A.: Radium in Treatment of Multilocular Lymph Cysts of Neck in Children, *Am. J. Roentgenol.* **21**:473, 1929.

cause pain, and there were no deaths attributable to the radium, in contradistinction to the reported fatalities after surgical treatment.

Each patient received from one to nine treatments, the average number being four. These figures, however, are only approximate, since some of the patients received further irradiation elsewhere. He reported that 3 of the 12 patients were entirely well, although in 1 of them a very small residual nodule, which might readily be excised, remained. Of the other 9, 2 were much improved and 7 died from an acute infection of the tumor. Four patients of the 7 had infected tumors when they first came under observation; it became necessary to establish drainage in 2 of them, in spite of which 1 promptly died. In 3 patients infection developed during the treatment, and death resulted.

Figi concluded from his experience that radium appeared to be of definite value in the treatment of multilocular lymph cysts in children, that acute infection did not occur more readily after radium treatment for hygroma and that the tumor might disappear or be reduced enough to permit surgical removal. In 2 instances, radium failed to reduce the size of the tumor permanently.

The arguments advanced by Figi for radium treatment in preference to surgical removal of hygroma are largely refuted by the experiences in the excision of hygromas reported in this series. There was only 1 fatality in these 12 cases, although 7 of the patients were infants. The fatal case was that of an infant with an enormous tumor of the right side of the neck, right shoulder and back (fig. 33).

Seven of the 12 patients in Figi's series died of acute infection of the tumor. Four of the 7 patients, to be sure, had an infected tumor when they first came under observation, but in the remaining 3 the infections developed during the course of the treatment. It is difficult to escape the conclusion that irradiation might have increased the severity of the infection in the former and lowered the resistance of the latter. It is well known that lymphatic tissues are peculiarly sensitive to irradiation and that their susceptibility to infection is increased by such treatment. There was only a single prompt recurrence of the tumor in the cases reported in this series. A second excision was followed by a complete cure (case 10).

Furthermore, the cosmetic result after surgical removal of the tumor is far better than that seen after treatment with radium. This is demonstrated in the photograph of the patient reported on by New.<sup>27</sup> Radium treatments had been given for four or five years at intervals of from two months to a year, and several periods of acute infection during the treatment had occurred. The ultimate cosmetic result was poor, for though there was a marked reduction in the size of the tumor, several

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27. New, G. B.: Cystic Hygroma of the Neck, *S. Clin. North America* 11: 771, 1931.

fluid escapes and the mass is likely to collapse, losing the definition of its peripheral margins. In several instances the contour and distention of the hygroma were preserved by immediate suture of the puncture. Preliminary injection of methylene blue, as recommended by Da Costa, was not employed, for if the entire operative field becomes stained by leakage of the dye, extirpation of the growth becomes more difficult.

The thin, almost transparent cysts are usually readily liberated, whereas the older, fibrotic, adherent portions of the tumor require sharp dissection. A pedicle or cord of fibrous connective tissue, occasionally containing edematous lymph glands, was seen in a few instances extending downward in the neck and attaching itself to the jugular vein near or at its junction with the subclavian vein. In no instance was a communication with the vein found even after careful search and probing. At times the deeper portions of the cervical hygroma were firmly attached to the mastoid process, the base of the skull and the transverse vertebral processes.

After complete excision in these cases, wound healing was uneventful. In most cases the wound was closed without drainage; in others drainage was required for only a few days. The cosmetic result was all that could be desired, and the operative scars were almost invisible. In only 1 case was there a postoperative infection of the wound. This occurred after an operation for a recurrence of the tumor and was secondarily due to intercurrent acute coryza and sore throat. Culture from the wound yielded *Streptococcus haemolyticus* (case 10). Incomplete excision may, of course, be followed by recurrence (case 10). In another case infection present in the neck at the time of the operation was responsible for slow healing of the wound and prolonged drainage. Cultures taken from the throat and the operative wound showed the presence of *Str. haemolyticus* (case 9).

The operative results, except in the fatal case and in the case in which there was mediastinal involvement, were excellent. The mediastinal extension in the latter case prevented more than partial excision. After this, roentgen therapy proved to be of considerable benefit. Nitrous oxide with the addition of small amounts of ether was the anesthetic used in all the cases, except those of very young children, to whom ether alone was administered. The youngest patient operated on was 6 months of age. Four patients were aged 3 years or less. Five were over 20, and the oldest was 40.

*Mortality.*—The mortality among children suffering with hygroma, as previously reported in the literature, has been strikingly high, and this seems to have been true regardless of whether the therapy employed included no treatment, a minor surgical procedure such as aspiration or incision, radium treatment or surgical excision. Statistics on the mor-

objection to surgical removal because of its dangers does not hold. Surgical treatment in most cases is to be preferred over radium therapy. Not only the patients failing to respond to the irradiation but even those showing distinct improvement must be subjected to subsequent surgical measures if cure is to be obtained.

*Ultimate "Follow-Up" Results.*—Late results following excision of hygromatous tumors were observed in 5 instances (cases 1, 10, 9, 7 and 5). In 1 patient (case 1), a slight postoperative weakness of the left half of the lower lip was noted, but this had almost entirely disappeared ten months later. There was a slight residual numbness over the area of distribution of the cervical nerves. The operative scar was practically invisible. No glandular enlargements were noted, and the child was in excellent health. There was no evidence of recurrence.

The tumor recurred five months after the first operation in case 10. One year after the operation for recurrence, there was no further trouble. There was residual hemiatrophy of the right side of the tongue, the result of division of the hypoglossal nerve at the time of the first operation. There was no recurrence, and the cosmetic result was good.

In the third case (case 9), the hygroma after its partial excision was subjected to high voltage roentgen therapy, which was continued for a period of six weeks after the patient left the hospital. Two treatments per week were given. Repeated films taken of the mediastinum finally showed practically complete disappearance of the mediastinal extension of the hygroma (fig. 47). There was some persistence of the swelling in the right submaxillary space, where several enlarged lymph glands were palpable. These were possibly remnants of the old trouble. In other respects, the condition of the patient appeared favorable, and there was no definite evidence of recurrence fourteen months after partial excision and roentgen therapy.

Neurologic pressure symptoms, the pains radiating to the back of the neck and to the ear and the paresthesia of the head and fingers, were relieved at once by operation in case 7. The sensation of choking and difficulty in swallowing disappeared. The right arm occasionally became fatigued after considerable use. There was no evidence of recurrence after three years.

Several examinations following the operation revealed no recurrence in case 5; the last examination was made ten and one-half years after the operation. The pressure of the tumor had interfered with swallowing, breathing and speaking to an extent which the patient had not realized before the operation. The cosmetic result was pleasing to the patient.

In 1 instance (case 2) the operation had been done too recently when the patient was last seen for one to speak of the ultimate result.

One patient (case 3) died in shock after a too extensive operation.

in the form of thin delicate membranes or streamers, grow out peripherally from the cyst walls. For a distance of 2, 3 or more millimeters they penetrate into the clefts of adjoining tissues, be they muscle, glands, blood vessels or nerves. Droplets of a lymphlike secretion similar to that in the adult cysts then arise within the fibrillae of the sprouts. This secretion is doubtless derived from the endothelial fibrillae themselves.

These droplets enlarge and cause the fibrillae to spread apart and canalize (figs. 19 and 20). In this fashion, new minute cysts with an endothelial lining acquired from the enclosing fibrillae originate. By continued secretion from the lining endothelium, these minute cysts grow to larger ones, and the fibrillae in the walls of these cysts continue distally into the adjoining tissues, to repeat the process. Fibrillar endothelial cords are seen to join the older cysts with the younger ones and to continue until lost in the more distant tissues, in a manner somewhat comparable to the growth of the banyan tree (fig. 17).

Examination of the zone immediately adjacent to the walls of the marginal cysts reveals constant microscopic attrition of the tissues as the hygroma eats its way, so to speak. Hygromatous stroma generally infiltrates this zone. A band of endothelial fibrillae, on meeting a tissue barrier, such as a small group of muscle fibers (figs. 9 and 10), divides to circumscribe and isolate it. The tissue thus isolated receives a covering of endothelial cells from the enveloping fibrillae. Between this cover and the peripheral fibrillae of the enveloping cord, a lymphlike secretion is formed from the endothelium, and in this manner a bundle of muscle fibers may be sequestered in a newly formed cyst lined by endothelium. The encysted tissue, as a result of pressure and interference with nutrition, undergoes hydropic degeneration and fragmentation and finally disappears by solution in the surrounding fluid of the engulfing cyst. Confirmatory evidence of this solution is apparent in the study of the cyst fluid, which in many instances has been found to contain remnants of fragmented, fatty-degenerated cells, conglomerate nuclei and cellular débris.

Individual tissue units, such as a muscle fiber, may be circumscribed, isolated and destroyed without the intervention of an engulfing cyst (figs. 29, 31 and 32). The individual fiber, surrounded by endothelial fibrillae, undergoes hydropic and fatty degeneration. Small droplets of fat appear within the muscle fiber. These coalesce to form large globules and finally replace the whole fiber, which then takes on the appearance of true adipose tissue. Groups of fibers transformed into fat form distinct areas of adipose tissue, commonly seen in the walls of the larger cysts and in the adjoining tissues. This resolution into fat represents a replacement of normal tissues destroyed by the hygroma.

## SUMMARY AND CONCLUSIONS

A detailed clinical and pathologic study of 12 cases of cystic hygroma is reported. In 10 of these the growth involved primarily the cervical region, and in 2, the axilla.

From a thorough review of the literature and a thoughtful consideration of the etiology of cystic hygroma, the plausible theory is that it arises from sequestrations of lymphatic tissue. In cases of cervical hygroma such sequestrations are derived from the primitive jugular sacs, which have failed to join the lymphatic system in the normal manner. Their potentiality of increasing in size to an almost unlimited extent is due to the fact that these "lymphatic rests" retain their embryonic power of irregular growth.

Predisposing or exciting causes are not known.

In the average case, there are no local or constitutional symptoms, although there may be cosmetic disfigurement. Symptoms may develop, however, in cases of advanced uncomplicated involvement, as a result of pressure on important structures, such as the trachea, pharynx and nerve plexuses. Severe respiratory embarrassment may occur when the tumor extends into the mediastinum. The large hygroma has a tendency to become secondarily infected, and the infection may be followed by serious symptoms or even death. Anemia and a poor nutritional condition are occasionally noted in children.

Hygroma is a benign, true neoplastic tumor of lymphatic origin. It is a multilobular, multilocular cystic tumor, the cavities of which are lined by endothelium characteristic of lymphatic spaces. The fluid content is usually clear or straw colored, occasionally turbid or blood stained. It is practically free of albumin or globulin and does not coagulate on standing. Various types of leukocytes, phagocytes, fragmented nuclei and cellular debris are noted in specimens which have been centrifuged; cholesterol crystals occur in cases in which there is hemorrhage. Lymphoid tissue, in fact, germinating centers, and possibly lymph glands are formed in abundance in cystic tumors.

Histologic evidence is offered as a basis for the explanation of the manner of growth, development and destructive action of hygroma. Endothelial fibrillar membranes or sprouts from the walls of the marginal cysts penetrate the adjacent normal tissues. A lymphlike fluid is secreted within the fibrillae, which are thereby caused to spread apart and canalize. Minute cysts with an endothelial lining are thus formed within these sprouts. By continued secretion within, the cysts enlarge; by pressure atrophy of the walls between adjoining cysts, the large cavities characteristic of hygroma are formed. The fibrillar membranes infiltrate and circumscribe adjacent tissues. Muscle fibers, nerves or other anatomic units are thereby sequestered and destroyed, either by direct atrophy

*Examination.*—The swelling on the left side of the neck (fig. 3) measured 8 cm. in the longest oblique diameter and 5.5 cm. in transverse diameter. It was as large as a medium-sized orange and presented a rounded, domelike swelling which occupied the region between the tip of the mastoid process and the angle of the jaw. The swelling extended down under the sternocleidomastoid muscle to the middle of the neck. The overlying skin was not attached. The swelling was soft and fluctuant, giving the impression of being filled with fluid. On pressure over the anterior portion of the tumor, there was a noticeable bulging immediately behind the posterior border of the sternocleidomastoid muscle. At the lower pole of the tumor, an enlarged lymph gland the size of a lima bean was felt; the mass was not tender. The swelling extended anteriorly almost to the midline. During forced expiration or movements of the head to the left against resistance, the tumor increased somewhat in size, while the left external jugular vein distended definitely and much more than the right. The tumor transilluminated well. The thyroid gland was barely palpable. The erythrocyte count was 3,200,000, the hemoglobin content 65 per cent and the leukocyte count 6,800. There were 65 per cent polymorphonuclears, 30 per cent small mononuclears, no large mono-



Fig. 3 (case 1).—A cystic hygroma of the left submaxillary and anterior cervical triangles. The tumor was first noticed when the child was 7 years of age. It grew rapidly in the beginning and later became quiescent. The hygroma extended from the mastoid process across the submaxillary triangle to the midline and downward almost to the sternoclavicular joint. It was firmly adherent to the vascular sheath, contained many thin-walled cysts filled with straw-colored, watery fluid and was associated with groups of hyperplastic lymph glands.

nuclears, 3 per cent eosinophils and 2 per cent transitional cells. The urine was normal. The preoperative diagnosis was hygroma of the left side of the neck.

*Operation.*—The hygroma of the left side of the neck was excised on June 27 with the patient under light chloroform and ether anesthesia. A horizontal incision was made on the left side of the neck 1 inch (2.5 cm.) below the angle of the jaw and over the most prominent part of the tumor. The greatly distended external and anterior jugular veins were ligated and divided. The surface of a thin-walled, cystic tumor giving a bluish reflex was uncovered and separated from the surrounding tissues, to which it was everywhere rather firmly adherent. The sternocleidomastoid muscle was gradually stripped away, and the tumor was outlined by careful blunt dissection. The tumor was situated under the sternocleidomastoid muscle and projected into the posterior triangle, upward almost to the mastoid process and forward and upward into the submaxillary triangle, anterior to the thyroid cartilage and hyoid bone. It thus occupied the greater portion of the



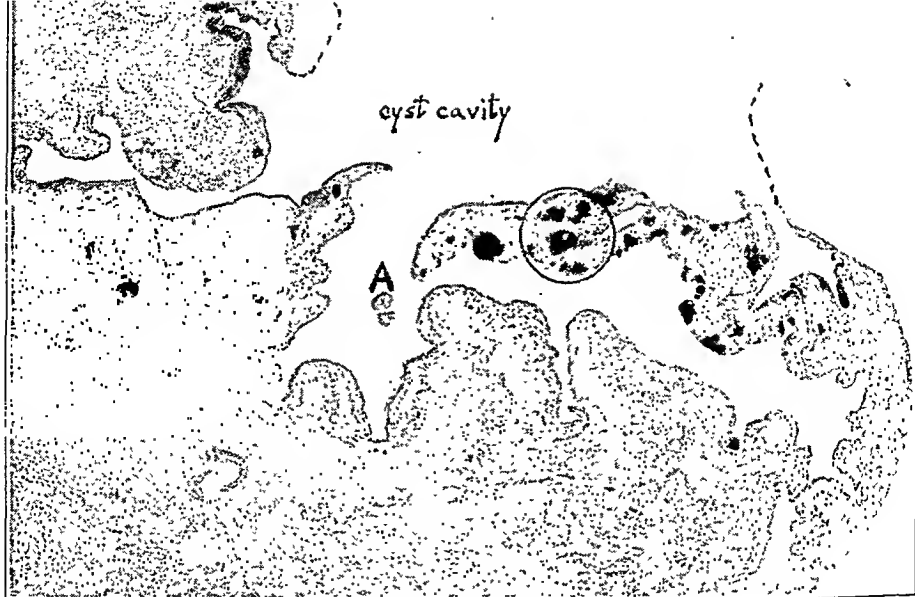


Fig. 4 (case 1).—A low power photomicrograph ( $\times 6$ ) of a section of a hygromatous stroma which forms the wall of a partially collapsed cyst. On the right is seen an intracystic papillary process containing dark aggregations of lymphoid cells and follicles. The bodies in the center, *A*, represent two occluded arteries. They have persisted as trabeculae traversing the cavity of the cyst after the partition in which these arteries were confined had disappeared as a result of pressure between two adjoining cysts.

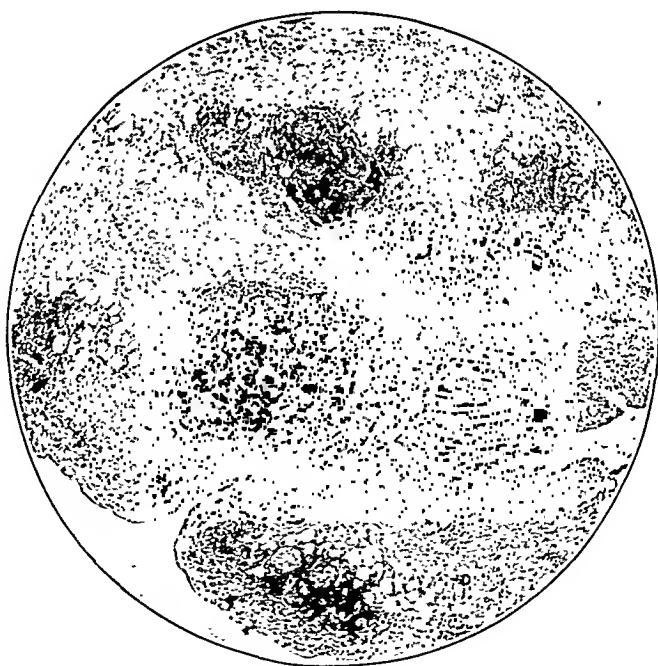


Fig. 5 (case 1).—A photomicrograph ( $\times 50$ ) of the area enclosed in the circle in figure 4. Numerous dense aggregations of lymphoid cells, often the antecedents of true lymph follicles, are shown, together with numerous small blood vessels. Note, toward the right, the peculiar structure consisting of cell cords with intervening slits, the nature of which is not clear. This area is shown in higher magnification in figure 6.

Opposite this papillary projection was found a thick wall lining the cyst. It appeared older, as was indicated by the rather broad zone of fibrillar, pink-staining connective tissue of hyaline type seen in low power in figure 7. The wall was lined by typical endothelium. In this thick wall of connective tissue were numbers of cells of the lymphoid, epithelioid and lymphoblastic type.

Below this dense connective tissue wall was a zone composed of a meshwork of loose areolar fibrillae and numerous small vessels. There was evidence of a rich proliferation of endothelium, which was forming small capillaries and lymph spaces (fig. 7).

Lying free in the cyst cavity were two rounded, isolated bodies which had an endothelial lining (figs. 4 and 8). The outer zone of each was composed of dense concentric layers of hyaline fibrillar connective tissue, and in the center of

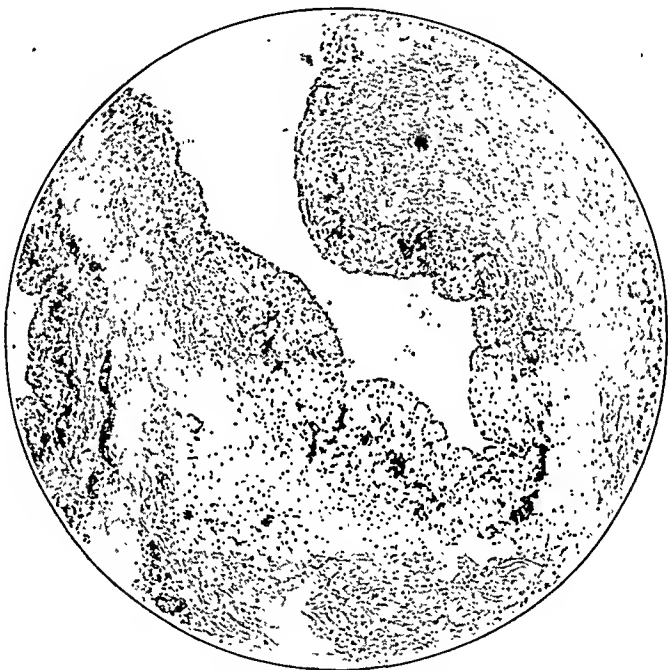


Fig. 7 (case 1).—A low power photomicrograph ( $\times 60$ ) of the wall of the cyst shown in figure 4. Note the endothelial lining, the thick hyaline connective tissue wall and below this a broad zone of delicate, fine fibrillar structure characteristic of the stroma of hygromatous tumors.

each there was a core of organized hyaline fibrous tissue, in which were seen a few small lymphoid connective tissue cells and the pale pink-staining lymphoblastic cells. Their outer surfaces were lined by endothelium. These bodies were interpreted as cross sections of trabeculae coursing through the cyst cavity, resulting from organization of thrombosed arteries persisting after atrophy of former cyst partitions.

Block III, Section *h*. Medium Power: This section, taken from an area adjoining a large cyst, showed the separation and isolation of muscle fibers produced by the ingrowth of endothelial fibrillar tissue. Many of the muscle fibers were atrophic and showed hydropic degeneration and beginning disintegration. A small cyst was seen, lined with endothelium which continued as a fibrillar streamer

In one area of the section, embedded in the spongy stroma, there was an isolated bundle of muscle fibers, of which some were swollen, pale staining and hydropic in appearance while others showed fragmentation of the fibrillae. The resulting fragments were homogeneous and glassy in appearance and had lost their affinity for stain. Surrounding and separating these fragments was the fibrillar connective tissue stroma.

Block III, Section *i*: This section represented an area much like that represented in section *h*. It showed very well the infiltration of the endothelial tissue between and around a small bundle of muscle. This bundle, similarly, lay sequestered in a cystic space. It showed well the gelatinous hydropic degeneration of muscle fibers, around which there was seen the characteristic fibrillar, endothelial tissue, as in section *h*.



Fig. 9 (case 1).—A photomicrograph ( $\times 175$ ) of an area adjoining one of the larger cysts. The section shows in its upper half the delicate fibrillar stroma and in its lower half bundles of muscle separated by the penetration of endothelial fibrillae. Many of the muscle fibers show evidences of degeneration. In the center is a small cyst enclosed in an endothelial envelop and containing dark-staining (hematoxylin) lymph. The cyst has completely surrounded and engulfed a bundle of muscle fibers, which are covered with endothelium and which lie free in the lymph. Note, at the right extremity of the cyst, a sprout of endothelial fibrillae continuing upward to enclose a nerve fiber, *N*. A small newly formed perineural cystic space is seen.

Block II, Section *a*. Low Power: The section, a longitudinal cut of a large lymph gland, showed a thick cortical zone and a relatively small hilus (fig. 11,  $\times 7$ ). The gland measured 1.3 cm. in longest diameter. Throughout the thick cortex were dense accumulations of lymphoid cells. In the hilus were large lymph spaces filled with lymphoid cells and numerous small blood vessels. The

striking feature of the cortical portion of the gland was the large number of lymphoid follicles with germinating centers. In the peripheral zone of the cortex the follicles were particularly large. The appearance was that of a hyperplastic lymph gland.

High Power: The germinating centers in this lymph gland had in general the same appearance as that described for the lymph follicles in the papillary projection (figs. 4 and 5). The cell types were essentially the same, namely the lymphoblastic, intermediate and lymphoid cell types (fig. 12). Furthermore, there were the large epithelioid cells and those resembling the endothelial type. There was a striking frequency of karyokinetic figures. A number of small capillaries were seen. There was a dense outer zone of lymphoid cells together with groups

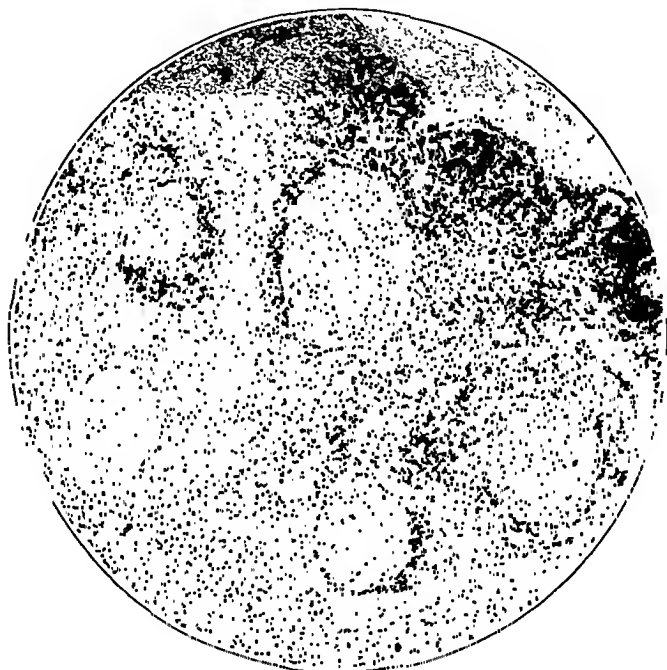


Fig. 12 (case 1).—A photomicrograph ( $\times 50$ ) of the area enclosed in the circle in figure 11. Note the large lymphoid follicles and the dense aggregations of lymphoid cells. Numerous lymphoblastic germinating cells with karyokinetic figures have been noted, not only in the follicles of the glands associated with hygroma but in the localized aggregations of lymphoid cells independent of true lymph glands. There is evidence that hygroma has the potentiality of producing isolated germinating follicles in all respects similar to those seen in lymph glands.

of pale-staining epithelioid cells, some lymphoblastic cells and numerous small capillaries. Endothelium was also seen, apparently forming new, small capillaries.

The hilus contained, besides the blood vessels and groundwork of connective tissue, large lymph sinuses, some of which were entirely filled with lymphoid and lymphoblastic cells and a few of epithelioid type. Plasma cells were frequent. Large blood spaces were also common. The appearance was that of a definitely hyperplastic lymph gland. Polymorphonuclear cells were hardly noted. The diagnosis was hygroma colli cysticum.

*Operation.*—The hygromatous tumor was excised on March 29, with the patient under nitrous oxide anesthesia. The cystic tumor was punctured, and about 20 cc. of a light brownish red, moderately turbid fluid was withdrawn. The incision was begun from a point immediately in front of the shoulder joint, extended downward medially and laterally to include a large lenticular area of skin, and continued almost to the fold of the elbow. Skin flaps were freed medially and laterally with great care in order to avoid rupture of the thin, bluish, transparent cyst walls. On the medial aspect, it was found that a thin layer of muscle derived from the biceps and brachialis anticus muscles was spread out over the tumor. A portion of muscle was allowed to remain adherent to the mass. The intercostal humeral nerves were sacrificed. The tumor was firmly attached to the lateral margins of the bicipital groove. These adhesions were liberated, as was a portion of the insertion of the pectoralis major muscle. The tumor did not extend into the axilla or along the great vessels, which were fully exposed. The limiting walls



Fig. 13 (case 2).—A photograph of a cystic hygroma of the right shoulder and upper part of the right arm of a boy 3 years of age. The hygroma was first noticed when the child was 3 weeks old, and it was then as large as a walnut. It enlarged progressively and reached the size of a grapefruit in three years. At the time of the operation it measured 16 cm. in length and 10 cm. in transverse diameter. Cystic prolongations of the tumor had penetrated and destroyed a large portion of the deltoid muscle. There were no symptoms, but the sheer weight of the tumor interfered with movements of the arm. A photograph of the gross specimen is shown in figure 14 *A* and *B*.

on the inferior aspect of the tumor were then easily freed from the humerus. Laterally, the margin of the triceps muscle came into view. The cysts were found to continue onward into the substance of the deltoid muscle (fig. 14 *A*, VI and VII). There were several finger-like, multicystic prolongations, penetrating and separating the muscle bundles in the anterior half of the deltoid. Consequently, in order thoroughly to eradicate this portion of the tumor, it was necessary to detach and excise the clavicular portion of the deltoid muscle. The upper limits of the hygromatous tumor did not appear to extend beyond the origin of the deltoid

the cysts (fig. 14 *A*, VII). Finally, the atrophic muscle fibers disappeared in the deeper, older portions of the tumor. A portion of this muscle had been definitely caused to atrophy by penetration and pressure of the cysts (fig. 14 *A*, VI and VII). One isolated cord or trabecula was seen enclosing a blood vessel of fair size containing a blood clot (fig. 14 *A*, III).

*Microscopic Examination.*—Blocks were taken from representative areas indicated by the numerals in figure 14 *A*, and sections prepared for microscopic examination.

Block II: A section from this area represented an area of tumor stroma of characteristic appearance. It lay between masses of muscle fibers. Strands or shoots of endothelial and connective tissue fibrillae were seen insinuating themselves between the muscle bundles. A serpentine cord of typical endothelial fibrillar tissue was seen coursing through the middle of the section. This cord or streamer

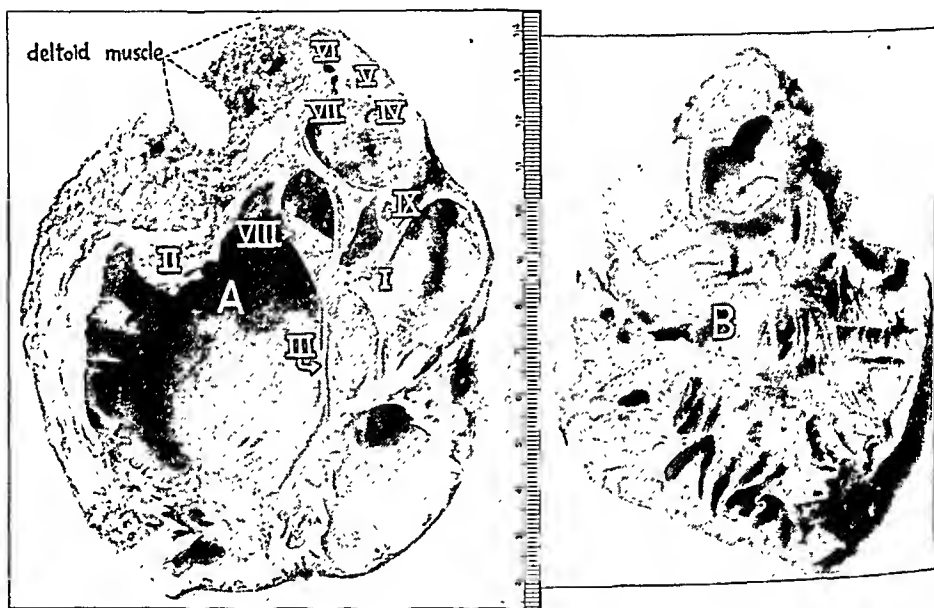


Fig. 14 (case 2).—*A*, the interior of the cystic hygroma shown in figure 13. *B*, the internal surface of the inferior wall or base of the tumor. The tumor, measuring 12 by 10.5 cm., was distended to natural size with solution of formaldehyde immediately after its removal in order to preserve the characteristics of the living tumor. Note in *A* the multilocular character of the cystic mass, the thin-walled and thick-walled cysts, some of which are intercommunicating, the remnants of the former partitions, the trabecula which contains an artery (area III) and the section of the deltoid muscle invaded by cysts (areas VI and VII). Note in *B* the inner surface of the base, showing perforated partitions, trabeculae and diverticula produced by the pressure of the cysts. The tumor contained a large amount of light brownish red turbid fluid.

was composed of a meshy, fibrillar stroma enclosed in endothelium. Within this cord were numerous small capillaries and cells of various types, recognized as endothelial, lymphoid, epithelioid and large mononuclear cells.

Block III: This area yielded a cross section of a trabecula which traversed the cyst cavity. It is visible in the photograph of the gross specimen (fig. 14 *A*).

blood vessels, lymph sinuses and accumulations of lymphoid cells. Running along in the center of the wall was a band of muscle fibers, which were compressed between the adjoining cysts, and which showed evidences of atrophy and hydropic degeneration. Areas of young connective tissue were seen, in which could be recognized newly formed capillaries, and the characteristic endothelial fibrillar tissue.

Block VIII. Low Power: A section (fig. 16) from area VIII (fig. 14 *A* and illustrated in fig. 16) showed the very delicate structure of one of the thin cyst walls, lined by endothelium on the outer surfaces and composed of loose, spongy stroma consisting of reticular, areolar, fibrillar connective tissue in which were

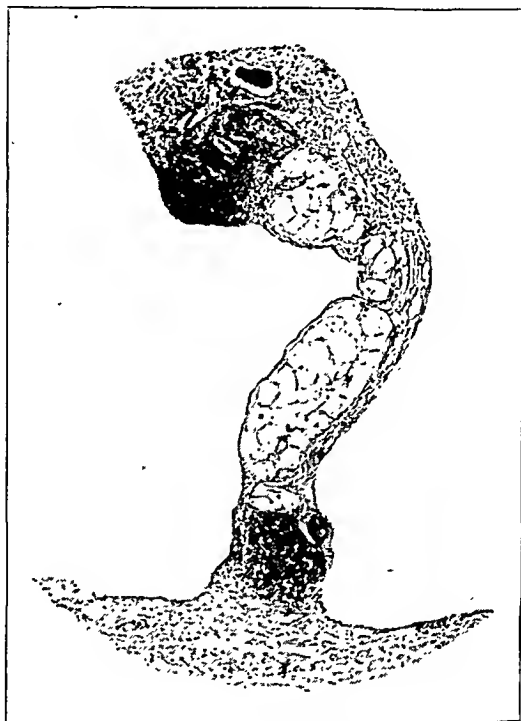


Fig. 16 (case 2).—A photomicrograph ( $\times 50$ ) of a representative section of a thin cyst wall (area VIII, fig. 14 *A*). Note the spongy stroma, the dense aggregations of lymphoid cells and the barely visible endothelial lining.

two fairly large, dense accumulations of lymphoid cells without germinating centers. Numerous small blood vessels were present in the wall.

High Power: Again the endothelial lining and the subendothelial delicate stroma, containing a number of blood vessels, accumulations of lymphoid cells and a few scattered epithelioid and large mononuclear cells, were observed.

Block IV, Section *a*: A section ( $\times 6\frac{1}{4}$ ) from this area (fig. 17) showed a small cyst at the margin of the hygroma and adjoining a mass of muscle fibers. The delicate fibrillar wall of the cyst may be seen in the upper part of figure 17. At the right border of the cyst, at *A* and *B*, a large area of hygromatous stroma penetrated, separating and destroying muscle fibers. Numerous dark-staining fibrillar serpentine streamers or sprouts, some of which are indicated by the

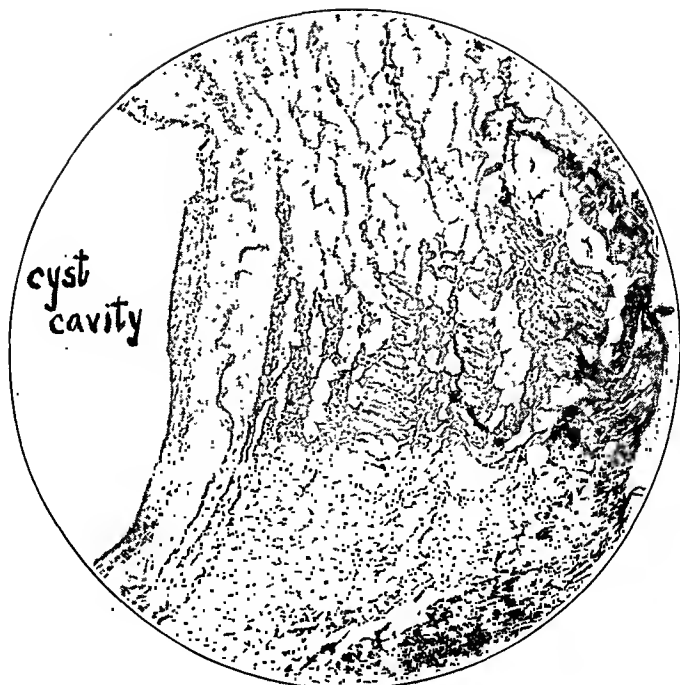


Fig. 18 (case 2).—A photomicrograph ( $\times 50$ ) of the area enclosed in the circle *B* in figure 17, illustrating some of the conditions found at the growing edge of a hygroma. Note the destruction of the muscle produced by the penetration of the tumor stroma between the muscle fibers.

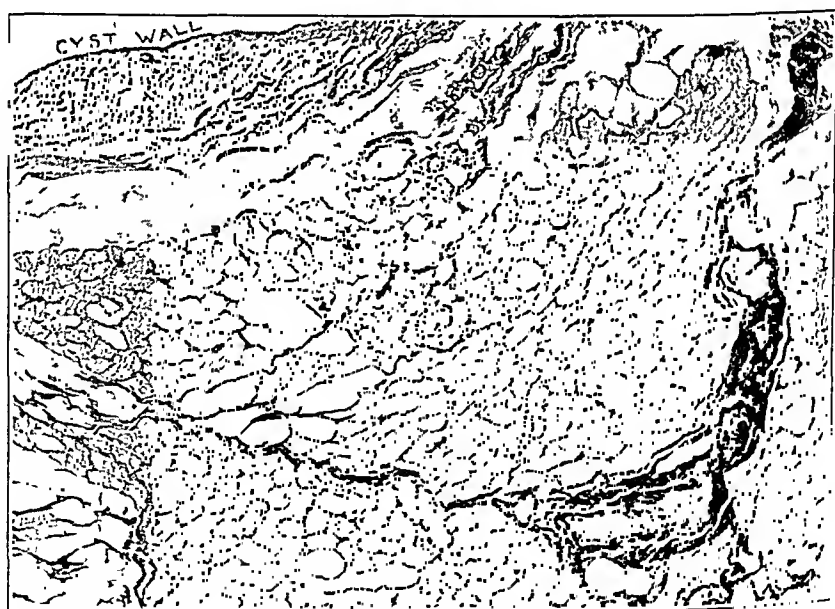


Fig. 18 *A* (case 2).—A photomicrograph ( $\times 85$ ) of a section from area IX, figure 14 *A*. The destructive action of the hygromatous stroma on an area of muscle is illustrated. Note the vacuolated appearance due to the disappearance of many of the muscle fibers and their replacement by fat, and the infiltrating fibrillar membranes.



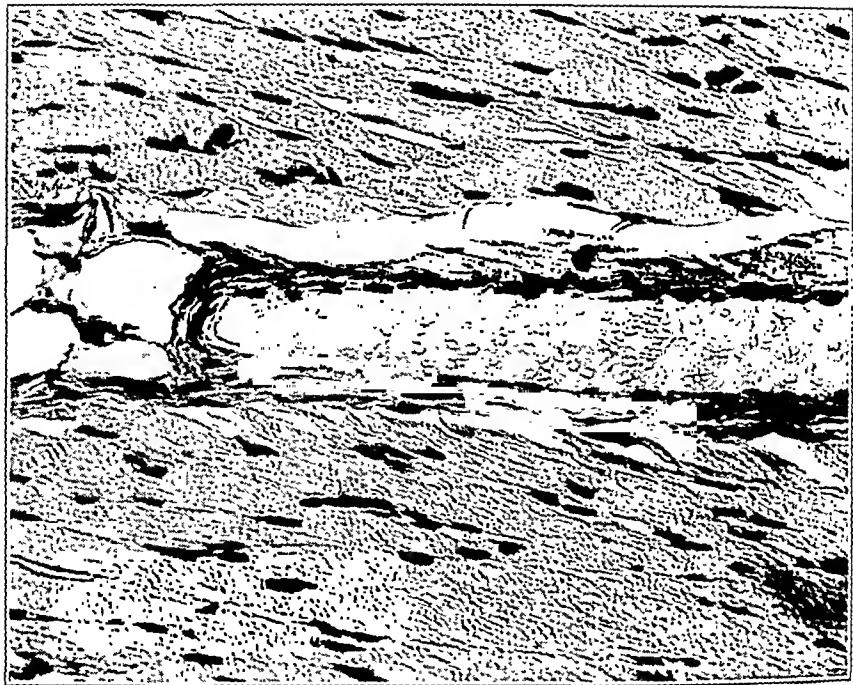


Fig. 20 (case 2).—A photomicrograph ( $\times 350$ ) of the cyst shown in figure 19. Note the endothelial lining and the spongy hygromatous stroma on the left, continuous with the endothelial fibrillar wall of the newly formed cyst. The adjacent muscle has not yet suffered from the growth and pressure of the cyst.

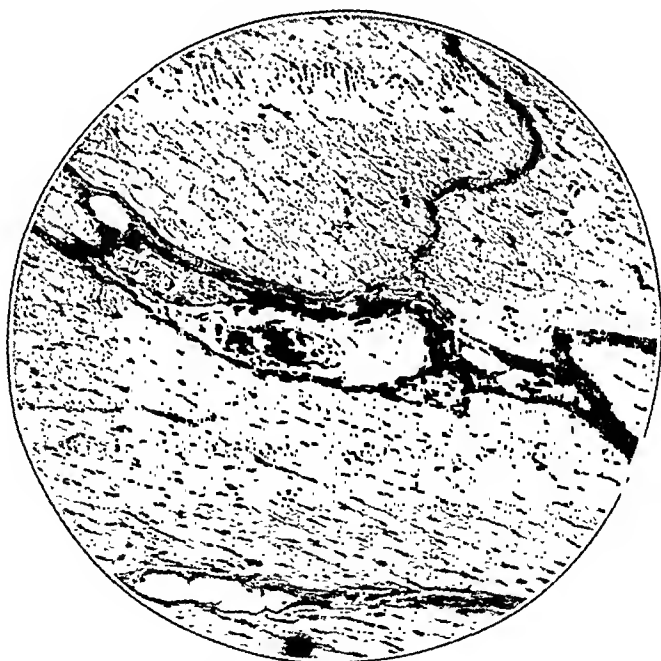


Fig. 21 (case 2).—A photomicrograph ( $\times 100$ ) of a section from area IV in figure 14 A. Endothelial fibrillar shoots are seen penetrating areas of muscle. In the center the fibrillae have been spread apart by secretion of lymph to form a new cyst, in which are seen remnants of tissue inclusions. Note the minute cysts at the extremities of the larger cyst.

middle of the section an irregularly shaped cyst. In the upper half, a large area of striated muscle fibers is apparent. The cyst was newly formed, thin walled and lined with endothelium. It contained frothy, blue-staining, semihomogeneous, coagulated lymph. Isolated and free in this lymph (enclosed in the circle in figure 23) were a number of fragments of striated muscle fibers. In the left half of the cyst are seen groups of conglomerate poorly stained nuclei, with small amounts of protoplasm, several large mononuclear cells, a few lymphoid cells and cellular debris. (These nuclei and cellular remnants were evidently the remains of degenerated tissue cells.)

Block VI, Section *b*: The photomicrograph in figure 24 shows the fragments of muscle fibers indicated within the circle in figure 23 to be poorly stained,

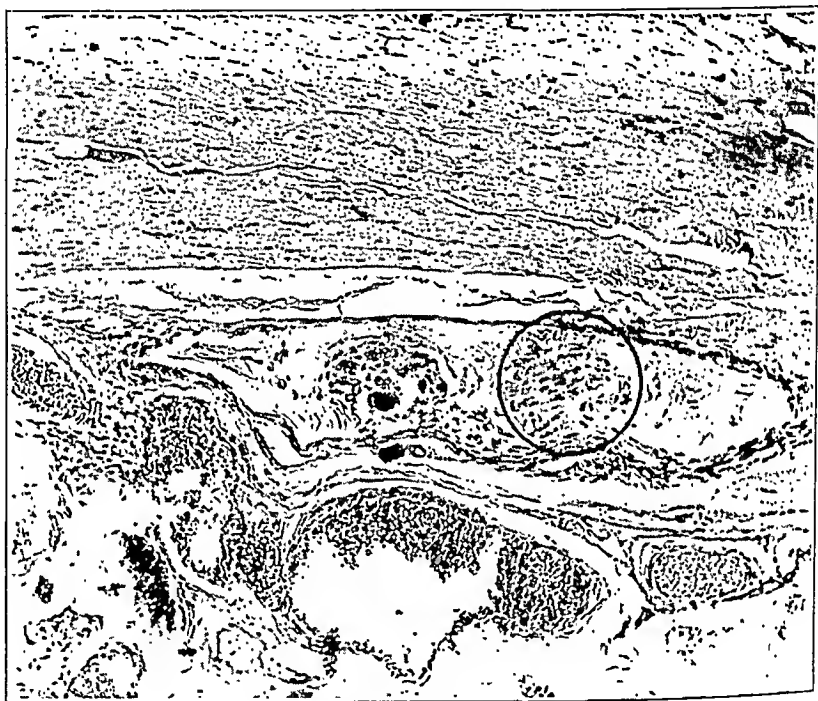


Fig. 23 (case 2).—A photomicrograph ( $\times 100$ ) of a section from area IV, figure 14 *A*, illustrating a cyst in hygomatous stroma adjacent to a mass of deltoid muscle. Note the isolated fragments of muscle shown within the circle and the remains of degenerated cells and nuclei to the left. Note the vascularity of the tumor stroma.

hydropic, shriveled and atrophic, with barely visible striations. The nuclei were swollen. In areas the muscle fibers were undergoing solution. In the cystic fluid around the fragments were a number of lymphoid and epithelioid cells.

Block VI, Section *c*: A section (fig. 25,  $\times 100$ ) showed masses of muscle fibers between which was hygomatous stroma. Incorporated in one muscle bundle was a thin-walled, irregularly shaped cyst. The muscle fibers immediately around the cyst were atrophic and frayed out. Enclosed within the cyst were isolated fragments of longitudinally sectioned light-staining muscle fibers.

Block VI, Section *d*: The cyst in the section described in the previous paragraph was seen in the higher power magnifications (fig. 26,  $\times 250$ ) to contain numerous striated muscle fibers in longitudinal section. Some of the fibers were lightly stained, had lost their striations and were undergoing a beginning hydropic degeneration. Endothelial cells were penetrating between the fibers. There were areas in which the fibers had undergone almost complete solution and were recognized as masses of granular débris. The endothelial lining and the fibrillar connective tissue in the wall of the cyst are well shown in figure 26.

Block VII: A section from area VII, figure 14 *A*, showed another area of muscle adjoining a cyst. Hygromatous tissue was seen penetrating the muscle and causing isolation, atrophy and fragmentation of the muscle fibers. Between the muscle fibers were seen endothelial and large mononuclear cells.

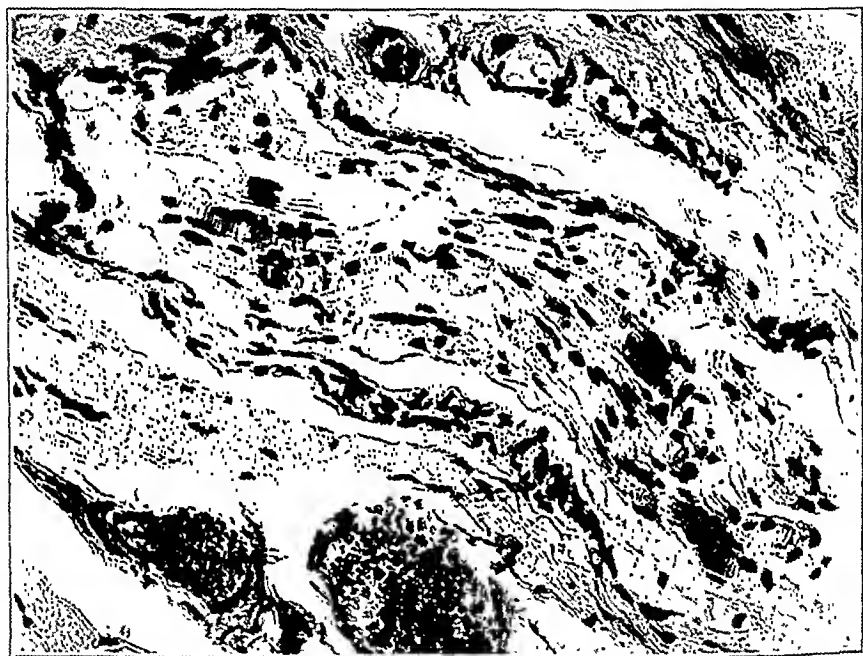


Fig. 26 (case 2).—A photomicrograph ( $\times 250$ ) of the cyst shown in figure 25. The details are here more apparent. The muscle fibers engulfed within the cyst are largely undergoing degeneration and fragmentation. In several, however, the striations are still preserved, indicating that the cyst is young and that the sequestration of these muscle fibers is a fairly recent event. The general character of the tumor stroma about the cyst is well illustrated.

Block VI, Section *c*: In section from area VI in figure 14 *A* (fig. 27,  $\times 150$ ) a mass of deltoid muscle fibers was in close proximity to the growing edge of the hygroma. There was some endothelial invasion between the muscle fibers, which showed transverse fragmentation, atrophy, poor affinity for stain, irregularity of caliber and almost complete disappearance of the striations. (This is a characteristic finding in voluntary muscle undergoing injury, as has been noted in a muscle infected with *Trichina*.)

Block VI, Section *f*: A mass of muscle fibers adjoining a cyst showed the separation and atrophy of the fibers produced by the penetration of hygromatous stroma (fig. 28,  $\times 100$ ). In the center of the photomicrograph one sees a small

bundle of muscle fibers surrounding a small cyst and several fragments of hydropic degenerating muscle fiber. Figure 29 ( $\times 350$ ) represents the same section as that shown in figure 28. One sees two fairly normal-looking striated muscle fibers separating to enclose a small cyst; a fragment of swollen, hydropic muscle fiber showing a loss of striations, and swollen fibrillae. The cyst and the fragments of muscle were surrounded by a fine membrane containing nuclei of the endothelial type.

Block IV, Section *a*: Van Gieson's stain showed a large area of dense muscle infiltrated with hygromatous fibrillar membranes (fig. 30,  $\times 85$ ). The latter stained a rich red, which sharply differentiated them from the surrounding muscle (yellow). A small cyst was formed within one of the fibrillar membranes and contained small fragments of muscle.



Fig. 29 (case 2).—A photomicrograph ( $\times 350$ ) of the muscle bundle enclosed in the circle in figure 28, consisting of two segments of muscle fiber confined within two fairly normal appearing fibers, the striations of which are barely visible. The segments of fractured fibers show hydropic degeneration and have lost their striations. Note the newly formed cyst, *A*, at the end of each segment.

Block IX, Section *a*: In figure 31 ( $\times 200$ ) dense zones of fibrillar stroma are seen between bundles of muscle. In the lower portion of the field (*A*) large globules of fat are seen in the membranes. This fat resulted from fatty degeneration of muscle fibers.

Block IX, Section *b*: In the lower portion of the field (*A*, fig. 32) the osmic acid stain showed rows of fat globules in the central axis of the muscle fibers. In the upper part of the field (*B*) these fatty fibers coalesced to form large areas of adipose tissue.

CASE 3.—J. P., a white boy aged 6 months, was admitted to the Long Island College Hospital on March 15, 1927, because of a tumor on his right shoulder since birth. He died March 18.

*History.*—There was no history of syphilis or tuberculosis. The birth was normal, the child weighing between 7 and 8 pounds (3,175.14-3,628.73 Gm.). He was breast fed, and his general health and appetite had been good. He had been gaining an average of 7 ounces (198 Gm.) per week. The tumor, which was noticed at birth, extended from the right ear over the shoulder and posteriorly over the back (fig. 33). It was somewhat larger than a grapefruit. The mother thought the mass increased in size when the child cried. The tumor had been aspirated when the child was 2 months old. It was reduced in size, but had since grown constantly larger. There were no symptoms. A clinical diagnosis of branchial cyst was made previous to the patient's admission.



Fig. 32 (case 2).—A photomicrograph ( $\times 45$ ) of a section from area IX, figure 14*A* (osmic acid stain), showing an area of compressed muscle, which adjoined a marginal cyst. Attention is directed to the longitudinally sectioned muscle fibers. In the central axis of several of these fibers, *A*, rows of fat globules are seen—an early stage of fatty degeneration. With further degeneration of muscle, these fat globules increase in number and size and replace entirely the muscle fibers. These fatty fibers, now transformed into fat, coalesce to form large areas of adipose tissue, *B*.

*Examination.*—The general examination gave negative results except with reference to the tumor. On the right side of the neck, extending from the ear, the ramus of the jaw and the midline across the shoulder and downward over the back and scapula, was a multilobulated cystic tumor which was sessile and could be shifted about to some extent. It was soft, fluctuant and nowhere red or tender. Certain of the lobulations of the tumor were definitely fluctuant and fluid containing, while others were firm and nodular. The overlying skin was thin and atrophic. The size of the mass caused the head to be carried well toward the left. The mass

and epinephrine. Dextrose solution was administered by rectum. All supportive measures failed, and the child died at 6:45 p. m. on the day of operation, as a result of shock and cardiac failure.

*Gross Pathologic Examination.*—The specimen, a tumor of the neck, measured 17 by 11 by 7 cm. (fig. 34). It was composed of a conglomeration of cysts varying from 0.5 to 6 cm. or more in diameter. The cysts were mostly thin walled; in certain areas they were transparent and in other areas they contained a considerable amount of white fibrous tissue. The inner lining of the cyst was smooth and glistening. The cyst contents were seen to be a clear straw-colored fluid, and a few of the smaller cysts contained some blood. They were bound together by a considerable mass of fibrous tissue, in which were seen large blood vessels. In

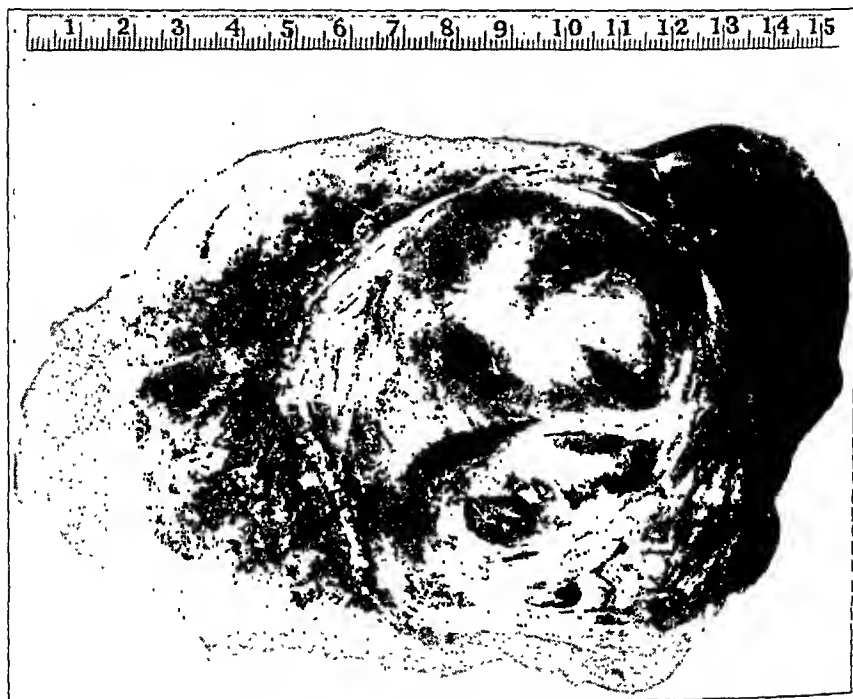


Fig. 34 (case 3).—A photograph of the gross specimen removed from the patient shown in figure 33. The mass was multilocular and composed of thin-walled cysts of varying sizes. There were firm areas in which there was abundant fibrous tissue. The fluid within the larger cysts was clear and straw colored, while several of the smaller cysts contained blood. The specimen measured 17 by 11 by 7 cm. One of the larger cysts has been opened, and the glistening wall shows trabeculation and numerous recesses.

one area was found a group of enlarged lymph glands, which on gross examination appeared normal.

*Microscopic Examination.*—The tissue showed enormously dilated lymph spaces of irregular outline and large dilated blood vessels. The cysts were lined by endothelium, and in the stroma surrounding the cysts were large accumulations of lymphoid cells. Heavy fibrous trabeculae were also seen. The appearance in general was much like that in the cases previously described (cases 1 and 2).

The systolic blood pressure was 108 and the diastolic 68. The erythrocyte count was 3,650,000, the hemoglobin content 78 per cent and the leukocyte count 15,200. There were 56 per cent polymorphonuclears, 32 per cent small mononuclears, 11 per cent large mononuclears and 1 per cent transitional cells. The examination of the urine gave negative results.

*Operation* (Dr. E. J. Browder).—The hygroma of the left submaxillary region was excised on June 20, with the patient under nitrous oxide and ether anesthesia. The old scar was excised, and the incision was extended downward along the anterior border of the left sternocleidomastoid muscle. It was soon evident that the swelling was a typical cystic hygroma which occupied the entire submandibular area, extended medially well beyond the submental area and the midline, occupied the entire left anterior triangle and extended downward to the episternal notch. Dissection was begun from the lateral aspects. The swelling was firmly adherent to the sternocleidomastoid muscle, a portion of which had to be excised in order to



Fig. 35 (case 4).—A hygromatous tumor in a Negro girl, aged 16. The mass appeared three years previously. Several incisions had been made externally and intraorally, followed by infection and prolonged drainage. The tumor reappeared after each incision. The hygroma involved the left submaxillary triangle, the floor of the mouth and the under surface of the tongue. The growth was far more extensive than one would anticipate from the apparent size before operation. It was unilocular and contained a thick mucoïd material, probably the result of previous infection.

be certain of removing the outer limits of the tumor. Medially, the mass was seen to be lying directly on the left lobe of the thyroid gland. The sternohyoid muscle was divided in order to liberate the extension of the tumor medially. A wide dissection had to be carried out in order to circumscribe the extensions of the tumor growth. Thus it was found necessary to remove the submaxillary gland together with a considerable number of enlarged adjoining lymph nodes, which were not only firmly adherent to the tumor mass but in several instances incorporated in it. The lower limits of the tumor reached almost to the episternal notch. The swelling was far more extensive than it was thought to be from the apparent size before operation. No definite pedicle connecting with the jugular vein was found. The

was no enlargement of the lymphatic glands on either side of the neck. The tumor measured 10 cm. in transverse diameter and 12 cm. in vertical diameter. There was no retromanubrial dulness, nor was there any dulness over the pulmonary apices. Examination of the heart, lungs, abdomen and extremities gave negative results. The pulse rate was 92 and regular. The radial pulse on the left was of good volume. The grip in the left hand was strong.

The erythrocyte and the differential count were within normal limits. The hemoglobin content was 90 per cent and the leukocyte count 1,300. The examination of the urine gave negative results. The preoperative diagnosis was cyst of the neck, of obscure origin and of benign nature, possibly of lymphatic or branchial cleft origin.

*Operation.*—On October 11, the hygromatous cyst of the left side of the neck was excised with the patient under nitrous oxide and ether anesthesia. A linear incision was made along the anterior border of the left sternocleidomastoid muscle from the angle of the jaw to the sternoclavicular joint. The anterior border of the muscle was dissected free and retracted. This procedure brought into view a bluish cyst with thin membranous semitransparent walls resembling serous



Fig. 36 (case 5).—An extensive cystic hygroma of the left anterior and posterior cervical triangles in a woman aged 34. There was a history of appearance of the swelling followed by disappearance over long intervals. The recent swelling was noted only four months previous to examination and had grown rapidly in size. There were no symptoms except a feeling of stiffness on movements of the head and neck. The mass extended from the mastoid process to the angle of the jaw, forward along the ramus of the jaw almost to the midline and downward to the left clavicle and the left sternoclavicular joint. The larynx and trachea were displaced to the right.

membranes. By careful division of dense connective tissue adhesions and by digital separation, delivery was made of the broad lower pole, which was hanging fairly free in the upper mediastinum. Anteriorly and medially the carotid artery and internal jugular vein were separated from the tumor. Dense adhesions were encountered under the sternocleidomastoid muscle and in the posterior triangle. The upper pole of the tumor was adherent and in intimate relation with several lymph glands situated below and anterior to the mastoid process. A small amount of watery fluid escaped from a perforation in the thin cyst wall. The upper pole with the adjacent lymph glands was then dissected free. After removal of the cystic mass, the upper and lower limits of the resulting cavity were touched with iodine to stimulate adhesions, with consequent obliteration. The cystic multilocular tumor contained a clear straw-colored fluid, on the surface of which cholesterol crystals could be seen. It appeared to be of lymphatic nature, and the



The temperature was 99 F. The erythrocyte count was 4,250,000, the hemoglobin content 85 per cent and the leukocyte count 7,200. There were 63 per cent polymorphonuclears and 36 per cent small and large mononuclears. The examination of the urine gave negative results. A preoperative diagnosis of cystic hygroma of the right wall of the chest was made.

*Operation* (Dr. Francis Clark).—The operation was performed on February 18, with the patient under ether anesthesia. The incision was begun just below the clavicle at the junction of its middle and outer thirds and was extended obliquely downward and laterally to about the costovertebral angle. In several places the cystic lobulated tumor was intimately adherent to the skin and was opened in making the skin incision. A clear fluid escaped. The mass was separated from the skin and the subcutaneous tissue by sharp and blunt dissection. Before the mass could be completely liberated an extensive dissection had to be carried

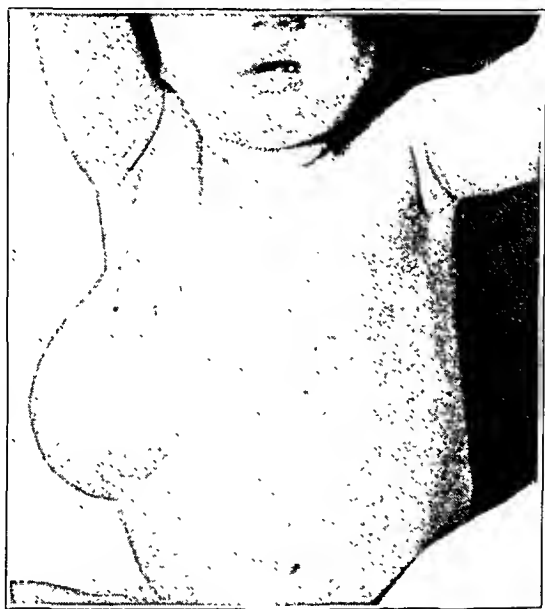


Fig. 37 (case 6).—A cystic hygroma of the right axilla and chest wall in a boy aged 13 months. The tumor was noticed at birth. It grew progressively larger but never caused any symptoms. The tumor was soft and fluctuant, transilluminated readily, measured 5 by 5 by 4 inches (12.5 by 12.5 by 10 cm.) and at operation was found to cover the anterolateral chest wall from the clavicle to the costal margin.

out, as the tumor was large and adherent to the anterior and lateral walls of the chest from the clavicle to the costal margin. No definite connection could be established between the upper extremity of the mass and the junction of the jugular and subclavian veins. The wound was closed and one drain placed under the skin flaps.

*Postoperative Course*.—There was no unusual postoperative reaction. A considerable amount of blood-stained serum drained from the wound. The sutures were removed on the seventh postoperative day. The wound healed well, and the child was in good condition one week after operation. He was discharged on March 7, 1931, seventeen days after operation.

about the size of a tangerine under the lower third of the sternocleidomastoid muscle. It projected into the posterior part of the supraclavicular triangle and extended from the origin of the sternocleidomastoid muscle outward to the outer third of the clavicle and posteriorly to the border of the trapezius muscle. The mass was definitely circumscribed, fluctuant and not tender and had a somewhat lobulated structure. It was not attached to the skin and was loosely attached to the deeper structures. The cervical lymph nodes were not enlarged. There was no retro-manubrial dullness. The examination of the heart showed numerous extrasystoles, and an electrocardiogram showed a perfect trigeminal rhythm. The auriculo-ventricular conduction time was normal. There were no abnormalities indicative of ventricular myocardial disease. No definite sensory changes were found in the right arm, but the grip of the right hand was not as strong as that of the left.

The clinical examination gave negative results with reference to pulse, temperature, urine and blood. The preoperative diagnosis was lipomatous tumor on the right side of the neck extending under the sternocleidomastoid muscle and projecting into the posterior triangle. The pain radiating to the back of the head and neck and to the right ear and the discomfort and numbness of the right arm were believed to be due to pressure on the nerves of the cervical and brachial plexuses.

*Operation.*—The hygroma was excised on June 20, with the patient under nitrous oxide and ether anesthesia. An incision was made horizontally across the posterior triangle starting at a point about  $1\frac{1}{2}$  inches (3.8 cm.) above the origin of the sternocleidomastoid muscle, and ending at the anterior border of the trapezius muscle. Very soon there appeared a tumor presenting a bluish reflex and the thin transparent walls characteristic of a hygroma. The fluid within was of a thin, watery, straw-colored, lymphlike character. Digital dissection was largely employed. The greater part of the tumor was liberated without difficulty. The anterior jugular vein, which was adherent to the anterior margin of the tumor, was separated from it and retracted medially. The mass was the size of a lemon and was attached by a number of strands at the junction of the internal jugular and subclavian veins. Otherwise the tumor was relatively free. No free communication with the subclavian vein could be demonstrated. The tumor was thereupon extirpated in toto. A small gauze pack was placed in the remaining cavity and the wound closed in layers with fine silk.

*Note:* The tumor consisted of one large cystic compartment and a number of smaller loculations. The posterior border of the tumor had been covered with a large pad of fat, characteristic of obese persons. It was this fat deposit which caused the lobulated feel and thus led to the tentative, preoperative diagnosis of lipoma. The tumor had rested directly on the cords of the brachial plexus which were seen in the bottom of the wound. The spinal accessory and phrenic nerves were both exposed and spared in the dissection.

*Postoperative Course.*—The patient made an uneventful recovery and was discharged on June 25, 1930, five days after operation. The wound was well healed.

*Gross Pathologic Examination.*—The specimen, a tumor of the neck, was composed of a large mass of adipose and areolar-looking tissue. In places there was a thin transparent membrane containing or enclosing clear fluid, possibly lymph. There was no structure present resembling a definite distended cyst or tumor. The walls of the cysts had largely collapsed.

*Microscopic Examination.*—A large block of tissue was preserved for microscopic study.

lymphoid cell core was itself covered by endothelial cells. In the outer portions of the section were large areas of extremely fine, delicate stroma. Minute fibrillae divided small, irregularly hexagonal areolar spaces; at the point of intersection of the fibrillae appeared the typical three-cornered cell, with a small amount of protoplasm and a well staining nucleus. In some ways this tissue, which was largely the ground stroma, resembled a very delicate adipose tissue. This condition was so common in the tissue in this case and in other cases described that it seems to be characteristic of the hygromatous stroma. There were also numerous blood vessels, lymphoid cell cords, lymph spaces and cells of various types in this stroma. The lymphoid cell predominated, however. There were some polynuclear cells and also some lymphoblastic cells. The tissue appeared to be young and growing. The diagnosis was hygroma colli cysticum.



Fig. 39 (case 7).—A photomicrograph ( $\times 50$ ) of the area enclosed in the circle in figure 38. Dense aggregations of lymphoid cells are seen, forming a central core within the walls of the cysts. Numerous small blood vessels are seen in this lymphoid tissue. Germinal centers, often found in hygromatous tumors, are here absent.

*Follow-Up Notes.*—July 7, 1930: Numbness was present over the upper part of the thorax and the lower part of the back.

Sept. 15, 1930: There were occasional sharp shooting pains through the right shoulder.

Oct. 2, 1931: No evidence of recurrence appeared. There was a very slight residual weakness of the right arm; this was much improved over the condition present before operation, however. The reflexes were normal. There was no evidence of the trigeminal rhythm which was present before operation.

May 6, 1933: The pain radiating to the back of the neck and right ear had been relieved. The paresthesia of the right hand and fingers, "falling asleep," had

Section 1. Low Power: A large, representative block of tissue showed an extremely delicate, loose, lacelike architecture, produced by folded and collapsed thin walls lining irregularly shaped large and small cyst spaces. The thin and delicate walls were lined by endothelium and composed of a finely reticulated fibrillar meshwork of connective tissue, such as was seen in previous cases. In one cyst a cross section of a process which is entirely composed of this reticular tissue was seen. It resembled an extremely fine adipose tissue. Some of the walls were older and fairly densely fibrotic.

High Power: The walls lining the cystic compartments were of varying thickness. Some of the thicker ones were composed of a fairly dense, wavy, hyaline, pink-staining connective tissue, containing few nuclei and numbers of lymphoid and epithelioid cells. The thinner walls were far more delicate in structure. They were more open and porous and composed of a loose, areolar, reticular framework which contained many small blood vessels and small aggregations of lymphoid and lymphoblastic cells, as well as epithelioid cells and occasional granular cells. The walls were everywhere lined by clearly stained endothelial cells. In the walls were seen connective tissue fibrillae, a few tissue cells and lymphoid and lymphoblastic cells. Here and there a small amount of adipose tissue was seen together with an occasional early beginning of a lymph follicle. The section was principally characterized by the extremely fine, thin cyst walls.

Section 2: This section was composed of a spongy tissue enclosing numerous spaces (fig. 40). There were several large blood vessels, both arteries and veins, and several fairly large irregularly shaped lymph spaces containing a coagulated secretion which stained lightly pink. The walls were fairly thick and composed of hyaline connective tissue. There was the usual well defined lining of endothelial cells. A few nerve fibers were seen. This section illustrated the rather marked vascularity of the hygromatous stroma which, in the form of a delicate, extremely fine, areolar network, surrounded this area. Another field showed a second large spongy area consisting almost entirely of small, irregular collapsed cyst spaces. The walls of the smaller spaces in this instance were dense and hyaline and contained a fair number of connective tissue nuclei, indicating, probably, a growing area. There were few blood vessels present. These small cyst spaces with heavy connective tissue walls contrasted strikingly with the very delicate meshy walls described in the first section discussed. Lymphoblastic cells were seen in the stroma around this area.

Section 3: This section resembled in many respects the two already described and showed even better the extreme fineness of the walls of many of the larger cysts (fig. 41). These walls, lined by endothelium, were composed of a delicate subendothelial connective tissue layer. The remainder of the wall was composed of the characteristic extremely fine areolar reticular connective tissue. Frequent occurrence of small blood vessels is also noted. Certain areas of heavy, dense, hyaline connective tissue trabeculae are seen. Papillary proliferations projected into cyst spaces, which in general were enclosed in a loose, meshy, hygromatous connective tissue of the fine areolar type. Lymphoid tissue and lymphoid follicles were conspicuously absent in this section. The diagnosis was hygroma.

*Follow-Up Note.*—May 6, 1933: No answer to the questionnaire was received. The patient could not be traced.

CASE 9.—C. F., a mulatto girl 5 years of age, was admitted to the Long Island College Hospital on Feb. 14, 1932, because of an infection of the upper part of the respiratory tract and swelling of glands of the neck. She was discharged April 15.

*History.*—The child was a "blue baby" and at birth weighed 10 pounds and 11 ounces (4847.76 Gm.). The delivery was at full term and normal. On her back was a supposed hematoma, which was drained. During the first few months, the draining wound kept the child below par. However, she gradually gained in strength and after the first year had very good health. A large swelling on the right side of the neck was seen at birth. It gradually increased until it reached the size of a grapefruit when the child was 3 weeks of age. The mass produced definite respiratory obstruction, which necessitated incision and drainage. The wound continued to drain for several weeks. Thereupon the swelling became much larger and more localized but did not produce respiratory embarrassment. During the succeeding years, the tumor diminished in size, and when the child was 4 years old it was as large as a lemon. After tonsillectomy at that time, the mass was said to have disappeared altogether. On February 10 the patient suffered an infection of the upper part of the respiratory tract, and soon thereafter the mother noticed a swelling at the site of the old trouble. Since that time there had been a gradual increase in size and extent of the mass. At no time had there been any external rupture with drainage. The temperature was intermittent, low in the mornings and as high as 103 to 104 F. every afternoon. The swelling noted at the time of admission resembled very much the enlargements described in previous cases.

*Examination.*—The patient was a fairly well nourished girl appearing pale and chronically ill. The skin was hot and moist. The cervical nodes on the left side were not palpable. The axillary and inguinal nodes were palpable. The head appeared massive in proportion to the remainder of the body. There was a tumor about half the size of a grapefruit on the right side of the neck, extending from the lobe of the right ear downward to the supraclavicular fossa. Anteriorly it extended 2 cm. beyond the midline, and posteriorly, to a corresponding distance. The mass was firm and elastic except for several soft cystic areas which were palpated in the lower portion of the tumor. The overlying skin was tense, pinkish at the borders of the mass and darker and adherent over the center. There was no tenderness. Several discrete nodules were felt in the mass. There were three short scars in the skin overlying the swelling. The trachea was displaced 3 cm. to the left. The mass itself did not seem to extend over the mandible but continued behind the ear and posteriorly to the lateral border of the sternocleidomastoid muscle and upward to about the middle of the helix. It filled the right side of the neck down to the middle of the clavicle. There was some limitation of movements of the head and neck caused by the size of the mass. The right side of the neck was definitely warmer than the left. The teeth were in poor condition, and the gums were spongy and infected. The tongue was coated, and the mucous membranes of the mouth and throat were beefy red and much inflamed. The mass on the right side of the neck had caused a bulging of the wall of the pharynx.

The following diagnosis was made in the pediatric department: (1) Vincent's angina or infection of the upper respiratory tract and (2) branchial cleft cyst with secondary infection.

The temperature for the first four days after admission varied between 100 and 103.8 F.; the pulse rate was 100 to 110, and the respiratory rate, 20 to 22. The erythrocyte count was 3,930,000, the hemoglobin content 56 per cent and the leukocyte count 26,950. There were 88 per cent polymorphonuclears, 10 per cent large and small lymphocytes, no mononuclears, no eosinophils and 2 per cent transitional cells. Wassermann and Kahn blood tests were negative. A culture of material from the throat taken on February 15 was negative for Vincent's organisms. However, a pure culture of hemolytic streptococci was obtained. A roentgen

February 29: A roentgen examination showed that the tumor had increased slightly in size as compared with the findings on the previous examination. The splenic tip had descended 2 cm. and was firm.

March 1: The tumor had increased markedly in size, especially behind the ear. On account of the marked anemia, a transfusion of 200 cc. of citrated blood was given. The roentgen diagnosis was a tumor, cervical and mediastinal, presumably malignant, on the right side, and cardiac enlargement. Roentgen therapy to the tumor was advised by Dr. A. L. L. Bell.

March 4: The temperature continued to be of the intermittent septic type. The tumor continued to increase in size, especially just below the ear and extending posteriorly below the occiput. The right ear drum was red and bulging. Jaundice was still marked.

March 5: There was a mass of infiltrated glands at the angle of the right jaw. This was exerting lateral pharyngeal pressure. The clinical diagnosis of acute suppurative lymphadenitis or lymphosarcoma and otitis media suppurativa was made. Paracentesis and drainage of the middle ear were advised.

March 6: For three days considerable edema and an area of fluctuation had been noted posterior to the operative incision. Six or eight cubic centimeters of a clear, yellow fluid which clotted quickly was withdrawn by aspiration. Since operation the wound had been discharging large amounts of serous fluid and had shown little tendency to heal. Between March 7 and 13, four exposures to high voltage roentgen rays were given to the tumor, which was tentatively regarded as a lymphosarcoma.

March 9: There had been some improvement since the roentgen therapy was instituted. The jaundice had diminished. The tissues of the neck were less boggy, and there was a noticeable decrease in the size of the swelling.

March 13: A transfusion of 180 cc. of citrated blood was given. Early pneumonic involvement of the middle lobe of the right lung was revealed by roentgen examination.

March 14: A roentgen examination revealed that the cervical mass was definitely smaller than it was on the previous examination.

March 15: The sixth roentgen treatment was given. The plate showed an increase in the pneumonic process with a definite fluid layer in the general pleural cavity on the right. The jaundice was less intense, and the liver was somewhat smaller. The general condition of the patient was fairly good.

March 16: A roentgen examination showed that the upper mediastinal shadow was still of considerable size. The conclusion from the roentgen findings was as follows: "While the lymph node in the cervical region has responded satisfactorily to radiation, and the upper mediastinal mass has responded to some extent, there seems now to be present a pneumonic process with a pleuritis on the right side. There is an increase in the mediastinal shadow due probably to fluid surrounding the tumor. For the time being at least, roentgen therapy must be discontinued." A diagnosis of sarcoma, cervical and mediastinal, and pneumonia was made.

March 17: The anemia had increased; the erythrocyte count was 2,970,000. the hemoglobin content 58 per cent and the leukocyte count 14,000. There were 88 per cent polymorphonuclears, 11 per cent large and small lymphocytes and 1 per cent mononuclears.

March 19: Since roentgen therapy was begun the tumor on the right side of the neck had markedly diminished in size. The collection of fluid on the right lateral and posterior aspects of the neck had almost disappeared. The operative wound was closing.

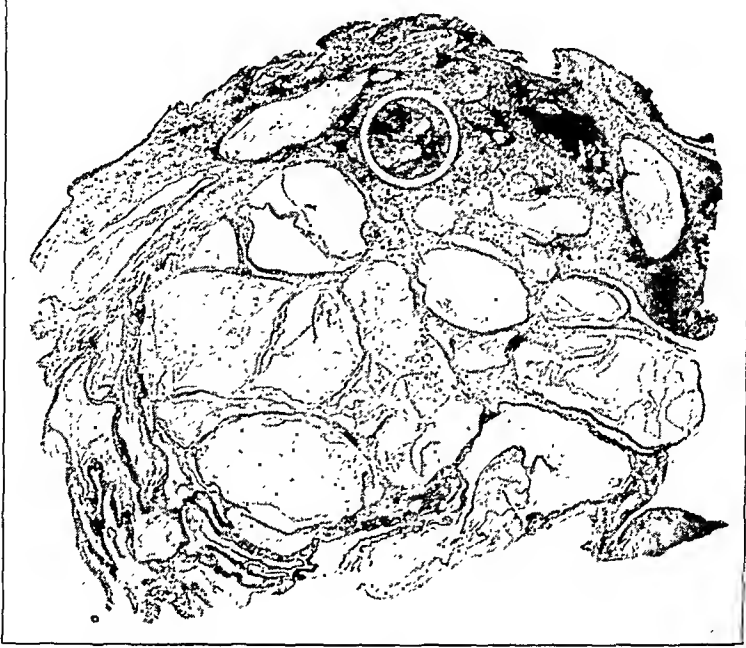


Fig. 42 (case 9).—A photomicrograph ( $\times 7$ ) of a section of hygroma, showing inflammatory reaction due to secondary infection with the hemolytic streptococcus derived from an "acute sore throat." In the upper right field the walls and cavities of the cysts are densely infiltrated with cells of inflammatory origin. The noninfected cysts in the lower field are clear and well defined, and their walls are extremely fine and delicate. The area enclosed in the circle is shown in higher magnification in figure 43.

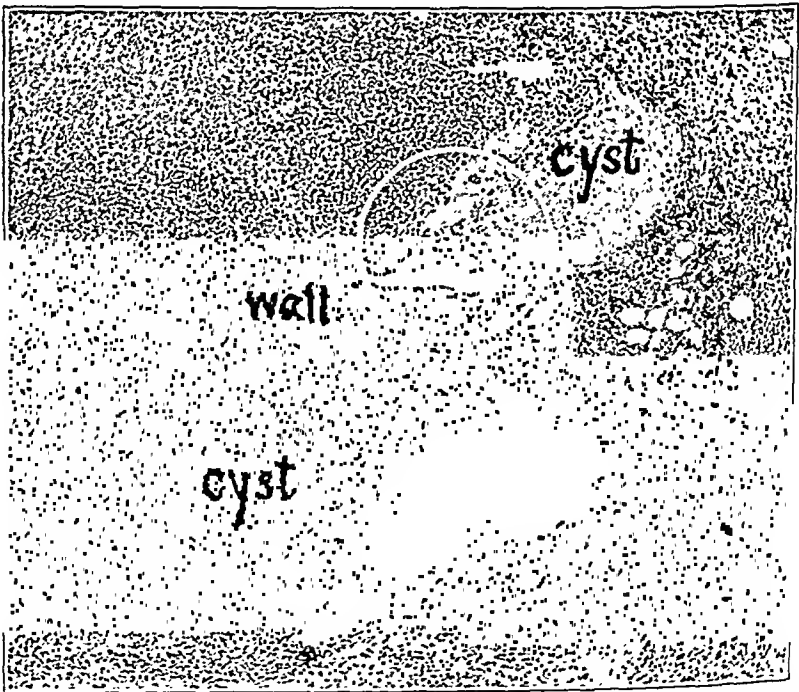


Fig. 43 (case 9).—A photomicrograph ( $\times 75$ ) of the area enclosed in the circle in figure 42. The two cystic cavities and the intervening wall are densely infiltrated with cells of inflammatory origin.



Fig. 45 (case 9).—A photomicrograph ( $\times 7$ ) of a section illustrating the spongy stroma often seen in hygroma. Note the innumerable small cysts and the broad zones of dense fibrous tissue below and to the left. The very dark areas between the cysts represent areas of lymphoid cell aggregations in the walls of the cysts.

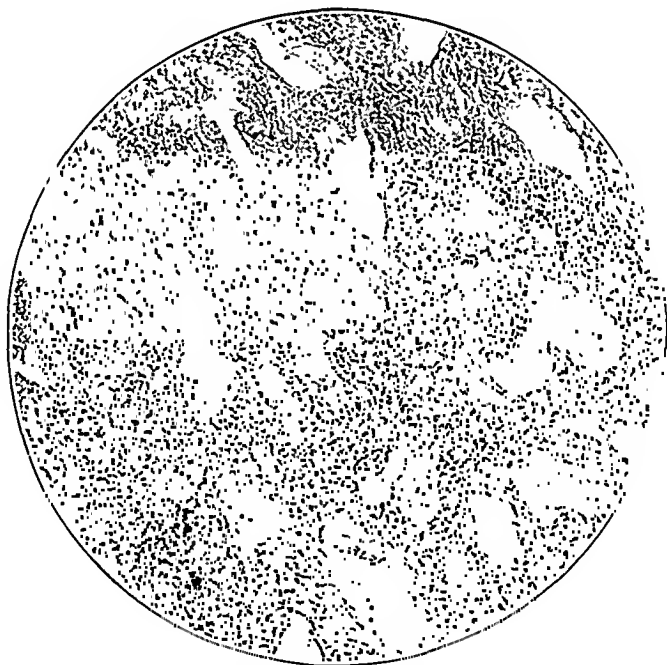


Fig. 46 (case 9).—A photomicrograph ( $\times 75$ ) of a section from the zone of small cysts shown in figure 45. The spongy character of the tumor, the lymphocytic infiltration in the walls of the cysts, and the denser accumulations of lymphoid cells are well shown. Germinating centers are not seen in this section.



(15.0 Kg.). At this examination her weight was 57 pounds (25.9 Kg.). A moderate pallor of the mucous membranes and face persisted.

Local examination showed an irregular, depressed scar running along the anterior border of the sternocleidomastoid muscle. There was no apparent swelling. A slight fullness was noted in the submaxillary space on the right as compared with the left side. There were several enlarged lymph glands to be felt in the submaxillary space. These glands were discrete and fairly firm. There was no mass and no cystic swelling anywhere. There was no enlargement of the glands in the anterior or posterior triangle on the right. On the left a few small glands were felt in the anterior triangle. The note over the manubrium was resonant to percussion.

There was some gingivitis, and the patient had lost several teeth. This was attributed to the numerous roentgen treatments. There was no bulging of the larynx, and examination of the throat gave negative results. There was no dyspnea, and

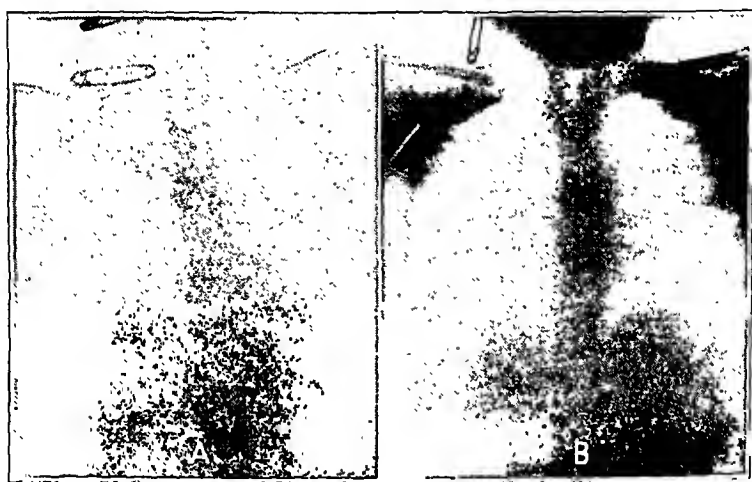


Fig. 47 (case 9).—*A*, roentgenogram of the neck and mediastinum taken on Feb. 24, 1932, before irradiation. The enlargement of the neck on the right side and the mediastinal shadow caused by the hygromatous tumor are clearly displayed. *B*, roentgenogram taken seven months later, on September 26. Prolonged and relatively intense high voltage roentgen therapy had been given. The photograph shows the diminution in the enlargement of the right side of the neck and in the extent of the mediastinal shadow as compared with the findings in *A*, before irradiation.

the voice was clear. The heart sounds were clear, and the pulse rate was 92 and regular.

There was no evidence of recurrence of the old condition. One point of possible significance was the fact that there was a group of moderately enlarged glands in the right submaxillary space. There was no edema or fullness of the tissues at the back of the neck.

The appetite was good. The child was active and appeared in good condition.

CASE 10.—D. S., a boy 16 months of age, weighing 22 pounds (9,979.02 Gm.), was admitted to the Long Island College Hospital on Nov. 5, 1925, and discharged on November 15. He had been born with a lump on the right side of his neck. This mass increased in size when he was a year old.

cysts at the base of the tumor, a small irregular body, 1 cm. in diameter, was seen. It had a vascular spongy appearance, and from its cut surface blood could be expressed. It was identified as a hemolymph gland. Strands of fibrous tissue extended in a radial direction from the center of the tumor to its capsule. Lying between these trabeculae were lobules of spongy-appearing tissue. Blocks were taken from the tumor proper and from the walls of the cysts for microscopic study.

*Microscopic Examination.*—The outer cyst wall was composed of fibrous tissue, covered by a thin layer of muscle and lined on its inside by a single layer of endothelial cells. The tumor proper was composed of a mass of loculated connective tissue, containing large numbers of cystic spaces and numbers of blood vessels of varying size. A spongy type of connective tissue surrounded the blood and lymph spaces. The diagnosis was hygroma.

*Second Admission.*—Soon after the operation done on November 16, the neck increased in size because of a cystic swelling in the right submaxillary region. This swelling gradually became larger until it resembled the tumor removed at the previous operation. On April 10, 1926, there was a large, bulging, soft, fluctuant swelling, resembling the original tumor, occupying the area below the ear and the angle of the jaw and extending into the submaxillary triangle. It was approximately 2 inches (5 cm.) in horizontal diameter and  $\frac{3}{4}$  inch (1.9 cm.) in transverse diameter. The mass felt cystic, and there were no nodules palpated in it. A general physical examination gave the same results as before. There had been no recurrence of the tumor in the area of the former operation. The clinical examination gave negative results.

*Operation.*—A secondary excision of the hygroma was performed on May 3 with the patient under ether anesthesia. The operative procedure was confined to the right anterior triangle, whereas the former operation was carried out in the posterior triangle. The dissection was long and tedious. The tumor was unusually extensive, having penetrated between and along practically all the important structures in the anterior triangle. The necessary dissection finally exposed the anterior jugular vein, vagus nerve, carotid artery, deep cervical lymph nodes and hypoglossal nerve and anteriorly the thyroid gland, to which the tumor was attached. The cystic mass extended above into the submaxillary space and posteriorly to the tip of the parotid gland, the mastoid process, the sternocleidomastoid muscle and the old scar. It was attached to, and involved, a large group of lymph glands in the deep midportion of the neck. These glands were removed with the tumor. The mass extended downward almost to the level of the clavicle in the form of a pedicle, which contained a large number of edematous-looking lymph glands. A thorough and extensive resection was done before it was felt that all the tumor had been removed. Another small cystic mass, which was enucleated from the submaxillary area and which seemed separate from the main tumor, was found to involve the submaxillary lymph glands. This portion resembled the major tumor. In the dissection of this area the hypoglossal nerve was unavoidably divided and subsequently sutured with fine silk. The wound was closed with drainage. The operation was well borne. An operative diagnosis of hygroma colli cysticum was made.

*Postoperative Course.*—May 3 to May 6: There was a good recovery from the operation. The protruded tongue deviated to the right.

May 9 to June 12: Acute purulent rhinitis developed, followed by infection of the operative wound, which had to be opened and drained. Culture of material from the wound yielded hemolytic streptococci. Following careful treatment of the wound and supportive measures for the patient, recovery was complete, and the patient was discharged in good general condition on June 12, 1926.

*Operation.*—The hygroma of the neck was excised on March 23, 1927, with the patient under nitrous oxide and ether anesthesia. A transverse incision was made over the most prominent portion of the swelling. Almost immediately the superior anterior wall of a cyst was exposed. The wall was exceedingly thin, relatively transparent and bluish and was described as "thin as tissue paper." The cyst wall was inadvertently punctured, and there was an immediate escape of a thin, pale, straw-colored, lymph-like fluid, previously seen in cases of typical hygroma. The incision was enlarged to allow a wide dissection. The cystic tumor was firmly adherent to the anterior border of the sternocleidomastoid muscle on the right and to the pretracheal muscles but not to the trachea. Consequently a portion of these muscles had to be included in the excision in order to be certain that the entire mass was extirpated. In other respects the tumor was readily liberated, there being no important structures immediately concerned. The wound was closed without drainage, fine interrupted silk sutures being used in the approximation of the platysma muscle, subcutaneous tissues and skin. The operative diagnosis of hygroma could be made from the gross appearance of the tumor.

*Postoperative Course.*—The patient convalesced normally; the wound healed per primam intentionem and the patient was discharged on March 29, six days after operation.

*Gross Pathologic Examination.*—The specimen, a cystic tumor from the neck, on section was seen to be trabeculated and multilocular. There were many larger cysts of varying size and numerous minute cystic cavities. There was one well defined lobule as large as a cherry. The walls of the cysts were frail and thin, and the lining was smooth and glistening. The contained fluid had the typical limpid, lymphlike appearance. Some muscle and adipose tissue were attached to the tumor.

*Microscopic Examination.*—Low Power: The section showed a large area of striated muscle adjoining a hygomatous cyst. The endothelial lining of the cyst appeared with a subendothelial zone of pink-staining, hyaline-appearing connective tissue. Below this, between this cyst lining and the muscle, was a wide area of hygomatous stroma of pink-staining, wavy, spongy appearance. This stroma contained relatively few nuclei and an abundance of small blood vessels and lymph spaces. The hygomatous stroma was seen penetrating into the planes between bundles of muscles. These penetrating bands of stroma were fibrillar in structure and contained elongated, flattened nuclei. There were wide areas of muscle fibers which showed poor affinity for stain and gave a glassy, hydropic appearance.

High Power: The cyst lining showed the usual type of endothelial cells, with elongated, flattened nuclei. The subendothelial zone was composed of fibers also supplied with elongated, flattened nuclei. The fibers of hygomatous stroma had a hyaline appearance. The neighboring muscle fibers showed a variability of appearance; in certain areas, the muscle fibers were swollen, hydropic and poorly stained; in other areas, longitudinally cut fibers showed rupture with transverse fracture, loss of striation and even fragmentation and degeneration to the point of solution. The hygomatous, fibrillar bands after penetrating between muscle bundles were seen to end by insinuating themselves in the form of minute fibrillar prolongations between the individual muscle fibers. The diagnosis was hygroma.

*Follow-Up Note.*—May 6, 1933: No answer to the questionnaire was received. The patient could not be traced.

CASE 12.—T. S., a housewife aged 42, was admitted to the Long Island College Hospital on Feb. 23, 1926, because of a swelling on the right side of her neck. She was discharged on March 6.

*History.*—She had had three children and two miscarriages. There was no history of serious illnesses. Six years previously, at the age of 36, the patient had

# PHENOMENA DUE TO MISDIRECTION OF REGENERATING FIBERS OF CRANIAL, SPINAL AND AUTONOMIC NERVES

## CLINICAL OBSERVATIONS

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The contracture of the facial muscles and the tendency to mass movements of the face which so often follow Bell's palsy have attracted the attention of neurologists since the earliest times, and a great many theories have been offered to explain these phenomena. Sir William Gowers<sup>1</sup> was inclined to ascribe the mass movements to a change in the functional state of the nucleus, and Oppenheim, who evidently held similar views, spoke of "irritation" of the facial nucleus. In 1906 Lipschitz<sup>2</sup> offered a more satisfactory theory when he claimed that the mass movements were due to misdirection of regenerating nerve fibers. Spiller<sup>3</sup> pointed out in 1919 that the same explanation might be offered for facial contracture. Various writers have attempted to explain the syndrome of crocodile tears and the auriculotemporal syndrome on the basis of misdirection of regenerating nerve fibers, and certain phenomena which follow regeneration of the third nerve have been ascribed to the same factor. As regards the regeneration of the spinal nerves, however, little application has been made of this theory. Surgeons have indeed suggested that when sensibility and motility fail to return after suture of the nerve misdirection of fibers may be to blame and have emphasized the importance of preserving the internal pattern of the nerve bundles as far as possible. It was not until Stopford's<sup>4</sup> paper appeared in 1926, however, that any effort was made to apply

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1. Gowers, W.: *The Movements of the Eyelids*, Med.-Chir. Tr. London 62:429, 1879.

2. Lipschitz, R.: *Beiträge zur Lehre von Facialislähmung nebst Bemerkungen zur Frage der Nervenregeneration*, Monatschr. f. Psychiat. u. Neurol. 20:84, 1906.

3. Spiller, W. G.: *Contracture Occurring in Partial Recovery from Paralysis of the Facial Nerve and Other Nerves*, Arch. Neurol. & Psychiat. 1:564 (May) 1919.

4. Stopford, J. S. B.: *An Explanation of the Two-Stage Recovery of Sensation During Regeneration of a Peripheral Nerve*, Brain 49:372, 1926.

do not always follow the same course that they pursued before operation. In cases in which two adjacent nerves are sectioned, the fibers may even enter the wrong nerve. One of Cajal's experiments may be cited in this connection. He severed the sciatic nerve of a cat at a point where it is composed of two separate nerve trunks, the peroneal and the tibial. The regenerating fibers of the tibial nerve entered the distal stump of both the tibial and the peroneal nerve, and those arising in the proximal stump of the peroneal nerve entered both distal stumps in the same way. Cajal<sup>5</sup> stated:

. . . those sprouts which reach the peripheral stump enter it in great disorder; some sheaths have no sprouts and the great majority, if not all of the sheaths, instead of receiving the outgrowth of the same axon which was present in them before the operation, are invaded by sprouts which have come from axons in other regions of the central stump. Thus, the observed facts compel us to reject the supposition of those authors who believe that the newly formed fiber infallibly ends in the old sheath of the peripheral stump and unerringly restores the old terminal arborization, thus preserving the anatomical and physiological individuality of the pre-existing conductor. On the contrary the errors and incongruences are so many that one wonders whether the whole mass of sprouts which penetrate into the peripheral stump is not entirely superfluous, seeing that the connections between central neurons and the peripheral structures which formed, since the embryonic period, such an intimate anatomical and dynamic whole, are now so disturbed and confused. Moreover, in cases of rapid nervous reunion after hemisection or complete sections with small scar, sensibility and movement are only more or less imperfectly restored.

It is universally admitted that certain changes occur in the nerve cells when their axons are divided. The cell becomes swollen, the nucleus is displaced and the Nissl substance and neurofibrils are broken up into fine granules. This process is termed the axon reaction. It seems to vary in intensity, depending on various factors such as the distance of the wound from the cell body and the severity of the trauma. It apparently is also more severe in certain nerves than in others. The process is a reversible one, and in cases in which the nerve ultimately regenerates most of the neurons so affected regain their original appearance and staining qualities. There is no evidence, of course, of any proliferation of nerve fibers in the spinal cord or in the posterior root ganglions in response to injury to their axons. In this connection Ramón Cajal<sup>5</sup> stated:

Concerning the restoration of central connections, it would be still more satisfactory to admit the re-arrangement or reorganization of pyramidal and sensory-reflex collaterals destined to rectify the aberrations of connection that have occurred in the periphery. But the dogma of the irregenerability of the central paths prohibits us from putting forth such a hypothesis.

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5. Ramón y Cajal, S.: *Degeneration and Regeneration of the Nervous System*, New York, Oxford University Press, 1928.

or the muscles and the muscles reacted by a slow and "wormlike" contraction when the galvanic current was employed. A complete reaction of degeneration was present therefore. The only therapeutic measure employed was gentle massage, and no electrical treatment was given. Within a few days the facial muscles became much relaxed. The lower lid fell away from the bulb, and tears ran over and down the cheek. The right corner of the mouth sagged, and the nasolabial fold and the wrinkles on the forehead were abolished. There was no evidence of improvement until the middle of March 1929, when the tone of the right side of the face began to improve, and soon after this the patient noticed some return of power. She was examined again in May 1929. A striking change had occurred. Tone was greatly increased in the affected side of the face. The right nasolabial fold was much deeper than the left, the right palpebral fissure was smaller than the left and the folds and wrinkles of the forehead were deeper on the right than on the left. The patient could close the right eye, move the right side of the mouth and wrinkle the right side of the forehead. It was evident, therefore, that the nerve had regenerated and that all the muscles had received motor nerve fibers again. However, all movements were grossly distorted. On repeated tests it was evident that whenever the patient moved any part of the right side of the face every muscle supplied by the seventh nerve on that side contracted to some extent. For example, when she closed the eyelid, the mouth was drawn to the right. When she showed her teeth, the right eyelid was partially closed. The muscles of the forehead were involved in both movements. On close inspection it was observed that every few seconds the right side of the patient's mouth would twitch spontaneously. It was easily determined that the twitching of the mouth was an accompaniment of the natural blinking of the eyelids. The blinking was not associated with any other movement on the left side of the face but was accompanied by a slight twitch of all the facial muscles on the right side. It was only the movement of the mouth, however, which was obvious enough to attract the examiner's attention. The state of tone of the right side of the face was not always the same. At certain times it was intense, and the nasolabial fold was deep. Again the face was perfectly symmetrical. During conversation, tone was almost always much increased, and it seemed to be nearly normal when the patient was quiet. The patient was requested to lie down, therefore, and to try to relax as completely as possible. Under these circumstances, the face was symmetrical for several minutes at a time. Reactions to electrical stimuli were normal.

The patient was told that the nerve had regenerated but that the nerve fibers had been misdirected to muscles other than those they had originally supplied. She was advised to try to regain control of the facial movements by exercises before a mirror. From time to time she reported that she was carrying out the exercises faithfully. At times she fancied that there was some improvement. Finally, in June 1935, seven years after the onset, the patient was examined once more. All the phenomena described were still present. It is possible that there had been a little improvement, but it is certain that there was no material change. All the associated movements were quite evident. There was still no true contracture of the facial muscles, for when the patient was relaxed the face was still symmetrical.

This case is not an exceptional one in any sense, and it would be easy to discover at least a hundred similar cases in our records. In our experience some evidence of mass movement and "facial contracture" is

For example, in a young woman recently examined who exhibited fully developed mass movements of the face following facial palsy, stimulation of the lower lip with a weak faradic current always resulted in contraction of a small group of muscle fibers above the eyebrow. Conversely, stimulation of the muscles above the eyebrow caused a flicker of the lower lip. The muscles of the eyelid and upper lip did not contract, showing that the current was not strong enough to spread over the face and cause this phenomenon by diffusion.

One might naturally inquire at this point why phenomena indicative of misdirection of regenerating nerve fibers are so obvious and so common in facial palsy and so inconspicuous in palsy of other peripheral nerves. The answer is to be found in the frequency of facial palsy and in the peculiar physiology of the facial nerve. It is probable that the facial nerve is paralyzed more often than any other nerve in the body. In a large percentage of cases it degenerates, and almost invariably more or less complete regeneration occurs. Facial palsy is usually a harmless condition, and the patient therefore survives. The face is so distorted that the patient almost invariably returns for further treatment in the vain hope of relief. The movements of the face are of extraordinary delicacy and of great importance in social life. The least change in facial movement or in tone of the facial muscles attracts attention at once. One reads faces so constantly that slight changes are recognized as changes in expression, even when one cannot analyze them as contractions of definite muscles. The significance of the movement is recognized without the movement itself being observed. The muscles about the eyelids are especially important in this regard, and the chief anatomic basis for changes in expression of "the eyes" is probably to be found in minute changes in the tone of these muscles. The least alteration of facial innervation, therefore, inevitably attracts one's attention.

It must be pointed out in this connection that the mass movements of the face and "facial contracture" occur in all cases in which the facial nerve degenerates and subsequently regenerates. They may be just as intense in cases in which the nerve has been paralyzed spontaneously, i. e., in cases of common Bell's palsy, as in cases in which the nerve has been sectioned and sutured. The anatomic basis of Bell's palsy is, of course, unknown, but it does not seem likely that the lesion can be such as to sever the nerve completely and destroy the relations of the various fiber bundles in the nerve in any gross anatomic sense. This observation, therefore, suggests that phenomena due to misdirection of regenerating fibers may be found in the peripheral nerves when the lesion is such as to leave the intrinsic nerve pattern intact.

*The Third Nerve.*—The third nerve supplies the levator palpebrae, the internal rectus, the superior rectus, the inferior rectus, the inferior

Bielschowsky<sup>7</sup> cited several cases similar to this one, and Bender<sup>8</sup> described an interesting case of the same type. In all of these cases there are features which frequently recur: 1. Certain movements of the bulb are absent. 2. The eye is frequently adducted when the patient attempts to perform some other movement. 3. The lid is elevated when the patient attempts to look downward or inward just as it is when he tries to look up. Bielschowsky and Bender agreed that these phenomena are probably due to misdirection of regenerating nerve fibers which arrive at muscles to which they do not belong. Bielschowsky suggested that the tendency for elevation of the lid to result from the impulse for adduction or downward rotation is due to the fact that the regenerating fibers prefer certain "routes" for growing in the wrong sheaths. We doubt that the regenerating nerve fibers follow any special route and wish to offer a somewhat different explanation for the phenomena described. Suppose that during the course of regeneration of the third nerve every muscle supplied by this nerve receives an abundant supply of neurons but that each muscle receives some of the fibers which formerly supplied every other muscle. Every effort to perform a movement in which the third nerve normally functions will therefore result in contraction of every muscle which receives its innervation from the third nerve. The attempt to look downward will cause contraction of the inferior rectus and of the superior oblique. No movement can take place in the vertical plane, however, for the superior rectus and the inferior oblique also contract at the same time. The internal rectus contracts with the other muscles, and since this is not opposed by any special action of the external rectus, the eye will be adducted. The lid will be lifted at the same time, for the levator has received some of the fibers which formerly innervated the superior oblique or the inferior rectus. When the attempt is made to look inward or upward, the same movements occur, for the same muscles contract, with the exception of the superior oblique. Abduction of the eye should occur normally if the sixth nerve is not involved. In this hypothetic case, therefore, we appear to find all the phenomena mentioned previously which seem to require explanation. It is likely that the loss of some movements of the eye in these cases may be due to simultaneous contraction of opposing groups of muscles rather than to failure of adequate regeneration. The tendency of the eye to be adducted when other movements are attempted may be due to the fact that the action of the internal rectus is not opposed by synchronous

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7. Bielschowsky, A.: *Lectures on Motor Anomalies of the Eyes: Paralysis of Individual Eye Muscles*, Arch. Ophth. **13**:33 (Jan.) 1935.

8. Bender, M.: *The Nerve Supply to the Orbicularis Muscle and the Physiology of the Movements of the Upper Eyelid, with Particular Reference to the Pseudo-Graefe Phenomenon*, Arch. Ophth. **15**:21 (Jan.) 1936.



thumb was always strongly adducted. This movement of the thumb might be somewhat inhibited by the contraction of the antagonists, but the muscle could always be felt to contract. Careful palpation revealed that when any of the intrinsic muscles supplied by the ulnar nerve were innervated, all of these muscles contracted to some extent. The muscles of the forearm which were never paralyzed did not take part in these abnormal movements.

*The Median Nerve.*—The following case history may be offered to illustrate the phenomena sometimes found in regeneration of the median nerve:

R. S., a young physician, received an injury in February 1932 which severed the left median nerve at the wrist. The nerve did not regenerate well, and a neuroma formed at the site of the lesion. In December 1933 the neuroma was removed by Dr. Dean Lewis, and the nerve was sutured. For a time there was complete loss of function with anesthesia of the usual distribution. Within two months, however, sensibility and motility began to return, although up to the time this report was written normal function had not been regained.

Examination on Nov. 3, 1936, revealed the following findings: 1. The left thenar eminence was smaller than the right, and the tip of the index finger was somewhat atrophic. 2. All the muscles of the hand supplied by the median nerve contracted to some extent, although their strength as well as their bulk was diminished. The muscles of the forearm were not affected in any way. 3. When the patient flexed or opposed the thumb, there was always definite abduction of the index finger and flexion at the proximal joint. At the same time the tendons of the long flexors grew tense. This we attributed to contraction of the lumbricalis muscle, which may cause abduction and flexion of the proximal joint and may also cause traction on the tendon of the flexor profundus digitorum. Conversely, strong flexion of the index finger was always associated with contraction of the muscles of the thenar eminence. 4. Tests with fine wisps of cotton revealed tactile sensibility to be intact. The threshold was no higher in the affected fingers than in the corresponding areas on the right hand. Warm and cool tubes of measured temperature were appreciated equally well on the two sides. The threshold for pain, tested with a weighted needle, was exactly the same for the two hands. 5. Tactile localization was grossly impaired when the test was made with a wisp of cotton wool. The most the patient could do was to guess which finger was touched. He was not always sure of the finger and could never recognize which joint or aspect of the finger was touched. On the right side he never failed to recognize the segment and aspect of the finger touched. When firmer pressure was made, the answers were more nearly correct. 6. Two point sense was greatly diminished, for the patient could not distinguish between one point and two when the tips of the compass were separated by 1 cm. and applied to the tips of the first and second fingers; whereas on the right, he made no errors when the tips of the compass were separated by 3 mm. The loss of two point sense was almost complete when light pressure was made and was less evident when the tips of the compass were applied firmly. 7. Stereognosis was much impaired on the left. Small letters carved from blocks of wood were employed. The patient was required to feel these with the first two fingers and the thumb. With the fingers of the right hand he recognized them instantly. With the fingers of the left hand he was unable to do more than guess and made about 50 per cent errors. He was able to guess correctly by running a finger over the outlines of the letter. 8. Pricking with a pin in the affected area caused a diffuse sensation of a peculiar nature over the entire zone of altered sensation. The same effect was produced

sensations of pain, heat and cold form connections with their proper end-organs, they will begin to function. On the other hand, regeneration of fibers concerned with tactile localization, two point sense and stereognosis will not lead to recovery, even if they chance to reach appropriate end-organs, because they will rarely if ever reach the same end-organs which they formerly supplied, and hence their function, which demands exact localization of stimuli, will not be restored.

The strange diffuse sensation which is characteristic of returning sensibility deserves some discussion. If one stimulates area A in a previously anesthetic area, one may well stimulate several neurons which formerly supplied areas B, C and D. The resulting sensations will naturally be referred to areas B, C and D, and the patient will experience feelings suggestive of multiple stimuli applied over a broad area. Strong stimuli, which may well be expected to stimulate several neurons, will cause such diffuse sensations, when touch with a single hair, which could scarcely stimulate more than one or two neurons, will not do so.

Stopford also offered an interesting explanation for the various perversions of sensibility sometimes found on examination of a patient during regeneration of peripheral nerves. If, for example, a burning sensation results when the patient is pricked by a pin, one may suspect that the stimulus has excited a "heat" fiber which has formed connections with a "pain" receptor. In the same way, the painful reaction to light touch or to scraping, which is sometimes observed, may be regarded as indicating that "pain" fibers have become connected with tactile receptors.

A number of authors speak of reeducation of the patient as if it were quite clear that it is possible for the patient to compensate in some way for the misdirection of peripheral nerve fibers. We are not convinced that this is possible. Certainly in the case of the facial nerve the mass movements and "facial contracture" are present throughout the rest of the patient's life without perceptible change. Head's famous experiment in which a nerve of his own forearm was sectioned and carefully sutured at once would seem to indicate that the power of reeducation in sensory nerves is negligible. Head stated: "But even at the end of five years after the operation, many errors of this kind are still present when the compasses are applied, even at a distance of 8 cm. over the abnormal area of the forearm." Head had made careful studies of sensibility in his arm during these five years, and if it were possible to reeducate oneself so as to compensate for such a defect in sensibility, one would imagine that he would have done so.

We wish to digress at this point to make a few remarks about the implications of the preceding statements as regards Head's theory of a dual system of sensory neurons. It is well known that he found in his experiments that cutaneous sensibility returns in two distinct stages

for example, which during the process of regeneration had reached some area of skin other than that it originally supplied, might function well as regards tactile sensibility but might at the same time have no value in those forms of sensibility depending on exact localization of stimuli. In our opinion the most striking dissociation of sensibility which is observed in the course of regeneration of peripheral nerves is not between protopathic and epicritic sensibility but is between all degrees of tactile, thermal and pain sensibility, which always return if the nerve regenerates satisfactorily, and tactile localization, two point sense and stereognosis, which do not return to even an approximately normal level. We believe that this type of dissociation is due to misdirection of sensory nerve fibers.

#### AUTONOMIC NERVES

*The Syndrome of Crocodile Tears.*—The commonest example of misdirection of regenerating autonomic nerve fibers is seen in the so-called syndrome of crocodile tears, which is not a rare sequel of a certain type of facial palsy. We may illustrate this condition by giving in abstract the history in a typical case.

J. McN., a healthy man of 68 years, had a severe pain in his left ear in May 1932. The next day he suddenly found that he could not close his left eye and could not move the left side of his mouth. His ear was inflamed, and there was some discharge from the external canal. The pain continued, and his family physician who had been treating him became alarmed and sent him to the hospital on the tenth day of the paralysis. Examination revealed complete paralysis of the left seventh nerve, with striking loss of tone of the facial muscles. The left eye was not obviously dry, but there was no overflow of tears despite the relaxation of the lower lid. There was an intense herpetic eruption in the concha and external canal of the left ear. Stimulation with an electric current resulted in the typical reaction of degeneration. The patient was not reexamined until September 1933. He then stated that he had not recovered movement in the left side of the face until at least ten months after the paralysis. At about the time power of movement returned in his face, he began to notice that every time he took food into his mouth tears would run from his left eye and down his cheek. Even the smell of food would make his eye grow somewhat moist. He never noticed excessive tear secretion under any other circumstances. This reaction never failed to occur when he was eating, and he was inclined to believe that it was more pronounced when he was eating food with a strong flavor. Examination revealed the associated movements and increased tone which have been described previously in cases of regeneration of the facial nerve. Lacrimation was easily produced by giving the patient chewing gum. The tears were visible within a few seconds after he began to chew, and within a minute they were running down his cheek.

The syndrome of crocodile tears may occur in several forms. The only type which is not excessively rare is that associated with facial paralysis. It must be pointed out that this syndrome does not occur in

is not eating, this area of skin is indistinguishable from the normal skin. One of us<sup>13</sup> has offered the following explanation for these phenomena:

The auriculotemporal nerve contains afferent fibers conveying sensory impulses from the skin, vasodilator fibers destined for the subcutaneous arterioles and secretory fibers for the sweat glands which are derived from the cervical sympathetic system. For a short distance near the parotid gland the nerve is accompanied by secretory and vasodilator fibers which supply the parotid gland and are derived from the ninth nerve by way of the otic ganglion. . . . It is evident, therefore, that when the nerve is injured between the parotid gland and the point at which it receives its communication from the ninth nerve the various groups of nerve fibers enumerated may be severed and, in the process of regeneration, may become misdirected along pathways other than those they originally pursued. It seems probable that the auriculotemporal syndrome is the result of misdirection of some of the secretory fibers of the parotid gland so that they form connections with the sweat glands and blood vessels of the skin. As a result, when the patient is eating and a volley of nervous impulses passes over the parotid fibers, paroxysmal sweating and vasodilatation occur in the distribution of the auriculotemporal nerve.

#### SUMMARY

We have attempted to show that various disorders of motility and sensibility which appear in the course of regeneration of the cranial, spinal and autonomic nerves are most easily explained by the assumption that the regenerating axons have gone astray and have formed peripheral connections other than those they originally possessed. This hypothesis is strongly supported by anatomic studies of regeneration which seem to show that regenerating nerve fibers rarely follow the course they formerly pursued. The mass movements of the face following facial palsy and similar disorders of ocular movements following palsy of the third nerve are cited in this connection. Several cases of lesions of the spinal nerves are described in which there were phenomena attributable to misdirection of the regenerating nerves. The auriculotemporal syndrome and the syndrome of crocodile tears are given as illustrations of misdirection of autonomic nerve fibers.

Dr. Frank Walsh supplied the illustrations.

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13. Ford, F. R.: Paroxysmal Lacrimation During Eating as a Sequel of Facial Palsy (Syndrome of Crocodile Tears), *Arch. Neurol. & Psychiat.* 29:1279 (June) 1933.

(3 plus). The Wassermann reaction of the blood was negative. The electrocardiogram revealed sinus tachycardia, left bundle branch block, a deep  $Q_1$  deflection and an inverted  $T_1$  deflection.

*Course.*—The next day the patient appeared worse and complained of a severe sticking pain in the left upper quadrant of the abdomen. The pain was never colicky and was not associated with nausea or diarrhea. The abdomen was not distended or rigid. There was exquisite hyperesthesia of the skin over the left half of the abdomen, especially the upper quadrant. Deep pressure did not increase the pain, and there was no rebound tenderness. No viscera or masses were palpable, and the hernial rings were normal. Enemas gave normal returns. The temperature was 103 F., and the white cell count was 14,300, with 87 per cent polymorphonuclear leukocytes. On the second day after the patient's admission the same findings were noted by the surgical consultant. The white cell count had risen to 23,500, with 92 per cent polymorphonuclear leukocytes. The patient became comatose and died forty-eight hours after admission. The final clinical diagnoses were: arteriosclerosis, hypertension and syphilis; enlargement of the heart, coronary sclerosis and coronary ostial stenosis with myocardial infarction; sinus tachycardia; cardiac insufficiency, as demonstrated by marked physical signs, even when the patient was at rest, and splenic infarction.

*Postmortem Examination.*—Autopsy was performed three hours after death. On section, the parietal peritoneum was smooth and glistening, and there was no free fluid. The viscera occupied their normal positions, and there were no hernias. The greater omentum, which measured 15 by 23 cm. and contained abundant fat, was free and showed no torsion or adhesion to any of the viscera. The left third of this structure was outlined sharply by its deep purple, lusterless appearance. This portion was thickened, firm and inelastic. On the posterior aspect, about 8 cm. from the attached end, a large branch of the left gastro-epiploic vein was completely occluded by a red thrombotic mass, which was adherent to the wall of the vein. Propagated thrombi were present in the smaller veins in the immediate vicinity. The walls of the veins showed no significant macroscopic changes. The arteries of the omentum were normal. Except for atherosclerosis of the abdominal aorta, the remainder of the abdominal vascular system was normal.

The gastro-intestinal tract and the mesentery were normal. The liver and spleen showed chronic passive congestion, the latter showing, in addition, a small organized infarct. The heart was tremendously enlarged, and there was a large healed infarct in the left ventricle and the interventricular septum. A mural thrombus, organized at its base but friable at its periphery, overlaid the infarct. All the coronary arteries were sclerotic, and the anterior descending branch of the left coronary artery was closed by an organized canalized thrombus. There was moderate aortic atherosclerosis. The lungs were edematous and contained patches of lobular pneumonia.

Microscopic study of sections through the omentum revealed extensive hemorrhagic infarction, with necrosis of the omental tissue. Almost all the veins were occluded by thrombi, composed chiefly of platelet columns with margined leukocytes and conglutinated red blood cells. No significant lesions of the walls of the veins were observed. The omental arterial system was normal.

#### COMMENT

This case is interesting from the pathologic as well as from the clinical standpoint. The facts that the occluded omental vessels were veins, that the corresponding arteries were patent and that there was

# EFFECT OF HYPOPROTEINEMIA ON WOUND DISRUPTION

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AND

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The rupture of abdominal wounds, with or without evisceration, is an old story. Even with the development of modern aseptic technic and a more intelligent handling of tissues, this complication continues to occur in from 1 to 3 per cent of all abdominal operations. Starr and Nason<sup>1</sup> found it in 0.61 per cent of their cases after laparotomy. Fincke<sup>2</sup> reported an incidence of 1.1 per cent; Meleney and Howes,<sup>3</sup> of from 1 to 2 per cent, and Eliason and McLaughlin,<sup>4</sup> of 0.27 per cent. Sokolov<sup>5</sup> reported an incidence in Europe of from 2 to 3 per cent. That this complication occurred in wounds which were not infected, in which hemostasis was good, in which trauma to the tissues and tension were minimal and in which unusual strain was obviated suggested that additional factors of a general character might be playing a part in the disruption of certain abdominal wounds. The fact that the majority of these accidents occur after operations on the upper part of the gastro-intestinal tract or on the biliary tract is significant. The mechanical factors incident to an incision in the upper part of the abdomen, the use of catgut, the tensile strength of which may rapidly decline, and

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1. Starr, A., and Nason, L. H.: Postoperative Rupture of Abdominal Wounds, *J. A. M. A.* **100**:310 (Feb. 4) 1933.

2. Fincke, cited by Horner, D. A.: Postcesarean Bursting of Abdominal Wounds, *J. A. M. A.* **93**:1126 (Oct. 12) 1929.

3. Meleney, F. L., and Howes, E. L.: The Disruption of Abdominal Wounds with the Protrusion of Viscera, *Ann. Surg.* **99**:5, 1934.

4. Eliason, E. L., and McLaughlin, C. W., Jr.: Post-Operative Wound Complications, *Ann. Surg.* **100**:1159, 1934.

5. Sokolov, S.: Das Aufplatzen der Bauchwunde nach Laparotomie mit Eventration bzw. Freiliegen der Eingeweide. Auf Grund eines Materials von 723 Fällen, *Ergebn. d. Chir. u. Orthop.* **25**:306, 1932.

## METHOD

In a previous paper we reported the type of diet which we used and the method of plasmapheresis employed in order to produce hypoproteinemia in the dog, together with the reasons for the use of this animal.<sup>7c</sup>

When the serum proteins were reduced to the level desired, the animal was prepared and anesthetized with ether anesthesia. An incision about 8 cm. long was made in each rectus muscle. The peritoneal cavity was always opened, and care was exercised that the incisions were of the same length and were made in exactly similar portions of the abdominal wall.

On one side the incision was closed with fine interrupted sutures of silk and on the other, with no. 1 chromic 20 day catgut the tensile strength of which had

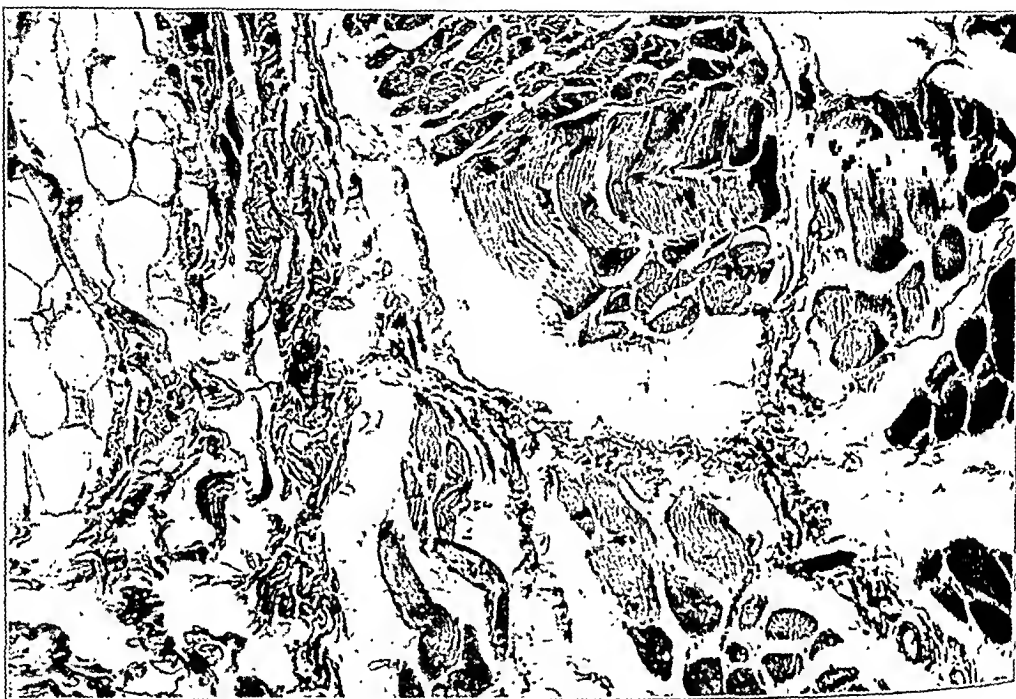


Fig. 1.—Tissue edema in a hypoproteinemic dog at the time of the abdominal incision.

previously been tested in our laboratory. The skin of each animal was sutured with silk. An exacting aseptic technic was employed on both sides, and sterile dressings and a binder were used to protect the wounds.

After operation the serum proteins were maintained at a low level, and biopsy specimens were taken from the wound on the seventh and the fourteenth post-operative day. The animals in which gross infection occurred were excluded from the study.

## RESULTS

In a series of eleven dogs disruption of the wound or a failure of the wound to heal during a hypoproteinemic state was observed eight times, an incidence of 72 per cent. Tissue was removed from four of the dogs for study at intervals of seven days. In others, serious infec-



Fig. 4.—Area of a wound in a hypoproteinemic dog showing the presence of a catgut suture. The catgut is undergoing disintegration, and there is an extensive cellular reaction around it.



Fig. 5.—Edge of a wound in a hypoproteinemic animal fourteen days after the original incision. There is marked tissue edema. A few fibroblasts are present.



fluid could easily be expressed from the surfaces of the wound even as late as fourteen days after the abdominal incision was made. The tissue around the site of the incision was edematous, glistening and pale, and the bleeding was not as great as would be expected from an incision at right angles to the original incision. There was no apparent attempt at union of the wound. It seemed as though the two surfaces were merely loosely approximated by the sutures and the serous material was interposed, keeping the surfaces bathed in a solvent which prevented even the sticky adherence found in very early sterile wounds. In the wounds sutured with catgut often only the remains of the knots were found, and in some of the disrupted wounds no catgut could be found. However, in the wounds sutured with silk the sutures were present, and these loosely held the tissues together.

In the sections taken from the skin, muscle, fascia and omentum at the first operation there was an evident intercellular edema (fig. 1).

In the study of the sections taken seven and fourteen days after operation, there was little difference, except that, perhaps, the tissue edema was even more prominent. Fibroblastic proliferation was found only occasionally in the seven day sections, indicating a marked delay in fibroblastic regeneration. In the fourteen day sections fibroblasts were observed but in greatly decreased numbers (figs. 2, 3, 4, 5 and 6). The histologic picture was that of marked delay in tissue repair.

#### COMMENT

The part which the plasma proteins play in holding fluid in the blood vessels has been amply discussed by numerous investigators. As the colloid osmotic pressure of the plasma proteins is reduced from its normal level, fluid leaves the vessels and passes into the intercellular spaces. The addition of large amounts of solution of sodium chloride intensifies the resulting edema.

Many of the patients coming to operation for abdominal lesions have suffered from severe nutritional deficits for some time prior to operation. The accompanying dehydration, which is so often present, may mask the true level of the protein depletion, but when the dehydration is overcome the serum protein may be at or below the critical level for edema. The trauma incident to the operation increases the edema at the site of injury, and the hypoproteinemia prolongs the secondary edema of the trauma. Furthermore, the administration of large amounts of solution of sodium chloride in the postoperative period, as previously stated, intensifies the edema. Thus, several factors work hand in hand to produce a condition which is inimical to satisfactory repair of the wound.

this group that the nonhealing wounds of animals or patients with hypoproteinemia and vitamin deficiency must fall. The explanation which we have advanced concerns but one of perhaps a number of such factors which may later be shown to influence repair. Lamnan and Ingalls<sup>18</sup> have shown that a vitamin C deficiency may also be a factor. Hypoproteinemia is one factor, however, which can in many instances be controlled in large part in the preoperative and postoperative periods. The vomiting to which certain of these patients with hypoproteinemia are subject may be in part due to a knuckle of bowel protruding into the wound but may also be due in part to the interference with the motility of the gastro-intestinal tract which such patients exhibit. The methods of correcting the hypoproteinemia in the preoperative and postoperative periods we plan to discuss in a subsequent paper. We have corrected the hypoproteinemia by repeated transfusions and by the use of a protein hydrolysate administered by proctoclysis.

#### SUMMARY

We have called attention to the fact that when every other factor which we could control, except hypoproteinemia, had been controlled, disruption of the abdominal wound still occurred in a large number of dogs after abdominal incisions. Healing of the wound was greatly retarded whether silk or catgut sutures were used, but actual disruption was greater with catgut. The failure of the wound to heal was, we believe, associated with the hypoproteinemic state, a condition which is present in many patients subjected to operations on the gastric, duodenal and biliary tracts.

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18. Lamnan, T. H., and Ingalls, T. H.: Vitamine C. Deficiency in Wound Healing, *Ann. Surg.* **105**:616, 1937.

In attaining this objective we have, we believe, employed a new method, in that we have used the plasma removed by plasmapheresis, which had been lyophilized and kept in the dehydrated state until just prior to its injection. The decline in the tensile strength of catgut in the normal and the hypoproteinemic dog was studied to determine whether the disruption of wounds so often encountered in these animals in our previous study might in fact be explained by an intermediate effect of the hypoproteinemic state on absorption of catgut.

Although Clark<sup>3</sup> first determined that restriction of proteins in the diet resulted in prolongation of the period of healing of the wound, the probability of a relationship between protein deficiency and disruption of the wound was not realized until this complication occurred a number of times in dogs in which the serum protein had been lowered to edema levels for the study of gastric emptying following various gastric operations.<sup>4</sup>

Since that time, we have attempted, before and after operation on the patient, to restore the serum proteins to a more nearly normal level when a deficiency existed. Fortunately, no instance of disruption of the wound has been observed, and as the concentration of the serum protein was not determined in former instances of dehiscence, it has not been possible to demonstrate the relationship statistically in man. The frequent occurrence of rupture of a wound after operations on the stomach and biliary tract and after surgical treatment for malignant growths of the gastro-intestinal tract and the high incidence of hypoproteinemia in the same group of patients strongly suggest that such a relationship exists. In many of these patients hypoproteinemia may be masked by dehydration and may not be evident until attempts are made to restore a normal balance of fluid and electrolytes.

In the work previously reported by us, every precaution was taken not to change any condition of the control experiments other than the deficiency of protein. We had observed healing of the wound after similar operations on normal animals and had studied the processes of wound repair when no protein deficit existed.

Care was taken to supply all other known dietary factors in adequate amounts to the hypoproteinemic dogs. However, as various secondary changes conceivably might result from or in association with the hypoproteinemia, we desired to determine whether the effects previously produced could be overcome by prompt restoration of the level of serum proteins after operation. The method we have used is not technically difficult and promises to be useful clinically.

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3. Clark, Admont H.: The Effect of Diet on the Healing of Wounds, *Bull. Johns Hopkins Hosp.* 30:117, 1919.

4. Mecray, P. M.; Barden, R. P., and Ravdin, I. S.: Nutritional Edema: Its Effect on the Gastric Emptying Time Before and After Gastric Operations. *Surgery* 1:53, 1937.

## RESULTS

In three dogs subjected to bilateral laparotomy during the hypoproteinemic state, disruption of the wounds or failure to heal was not observed when the hypoproteinemia was controlled, after abdominal incision, by intravenous infusion of lyophile plasma.

At the time that the incisions were made, the tissues were paler than normal and looked as though a local anesthetic had recently been injected (fig. 1). In one dog there was approximately 1,000 cc. of ascitic fluid in the peritoneal cavity. In another the omentum was markedly edematous. The wounds at the time of the first biopsy after the abdominal incisions were somewhat drier than at the first operation, but were still moist (figs. 2 and 3). At the end of seven days the serum proteins were normal in each instance. The wounds appeared grossly to be healing normally. On the fourteenth postoperative day, at the time of the second biopsy, the wounds appeared grossly to be normally healed (figs. 4 and 5). The wounds at the time of the first and second biopsies had no similarity to those observed in hypoproteinemic dogs except moderate moistness, which was observed at the first biopsy. Considerable fibroplasia was grossly evident seven days after the abdominal incisions.

Determinations of total serum proteins gave values below the critical level for edema at the time of the original laparotomy and were elevated to within normal limits in seven days after six venoclyses of plasma. This level was maintained or elevated for the second period of seven days with four venoclyses of plasma.

In the sections taken from the skin, muscle, fascia and omentum at the time of the original abdominal incision there was evident intercellular edema (fig. 1).

In the sections taken on the seventh day some intercellular edema was still evident; however, there was definite evidence of fibroblastic proliferation and healing of the wound. The area of the newly forming scar was filled with new capillaries (figs. 2 and 3). The sections of the tissue removed on the fourteenth day revealed firm fibroblastic repair, and the intercellular edema had disappeared (figs. 4 and 5).

The mean decline in the tensile strength of no. 1 chromic catgut placed in the dog's abdominal wall for four days when the serum proteins were normal was 40.7 per cent, while the mean decline of the same type of catgut in the same dogs after development of hypoproteinemia was 55.6 per cent. It was our impression that the animals were much more susceptible to infection at the point where the catgut protruded through the skin during the hypoproteinemic phase. It is therefore impossible to be certain whether the more rapid decline in the strength of catgut during this phase was due to this factor or to the hypoproteinemia per se.

means of correcting, temporarily at least, the hypoproteinemic state. The lyophile process of preserving plasma described by Flosdorf and Mudd<sup>7</sup> provides plasma in such a state that it can be shipped to isolated communities and kept for months at refrigerator temperature for immediate use. In addition to these advantages, it can be given intravenously



Fig. 4.—Section ( $\times 200$ ) through a fourteen day old wound, showing well developed fibroplasia with excellent wound healing.

as a hypertonic solution. This has two merits: Not only does it rapidly replenish the protein deficit, but, being given as a hypertonic solution, it

7. Flosdorf, E. W., and Mudd, Stuart: Procedure and Apparatus for Preservation in "Lyophile" Form of Serum and Other Biological Substances, *J. Immunol.* 29:389, 1935.

From the results of our experiments with catgut, which showed that decrease in the tensile strength of the catgut increases with the degree of hypoproteinemia, it seems advisable to use a nonabsorbable suture material in cases of protein deficiency. If this is inadvisable because of fear of infection, the layer sutures of catgut should be reenforced by stay sutures of nonabsorbable material.

#### SUMMARY

1. Retardation in healing of wounds associated with hypoproteinemia in dogs may be averted by restoration of the serum protein to normal levels immediately after operation.
2. The decline in tensile strength of catgut in dogs was accelerated by induction of hypoproteinemia, although this may have been due in part to the greater tendency to infection at the junction of the skin and catgut.
3. The advantages of lyophilized serum or plasma for restoring the concentration of the blood proteins are pointed out, and the practicability of the method is demonstrated for dogs.

90 diastolic; hemoglobin content, 53 per cent; red blood cells, 2,600,000; white blood cells, 7,800, with a normal differential count; Kahn and Wassermann reactions negative, and urine, normal.

On the basis of the large tumor mass, which had recently enlarged, the loss of weight, the secondary anemia, the cachectic appearance of the patient, the persistent cough and the suggestive pulmonary lesions, the diagnosis considered most likely was fascial sarcoma of the right inguinal region with metastases to the lung. This diagnosis was practically discarded a few days later when the tumor was aspirated and 210 cc. of clear, viscid yellow fluid was drawn off. The tumor refilled within ten days. Culture of the fluid was sterile. A guinea-pig inoculated with the fluid was killed after six weeks; no pathologic changes were found at autopsy.

In view of these findings, an exploratory operation was performed on Feb. 7, 1936, just thirty years after the tumor was first noted. A 1 per cent solution of procaine hydrochloride was employed as a local anesthesia, and an incision was made parallel and lateral to the femoral sheath. The skin, subcutaneous tissues and thinned out layers of the sartorius and iliopsoas muscles were retracted. A firm white fibrous capsule formed the external wall of the tumor. On incision, 500 cc.

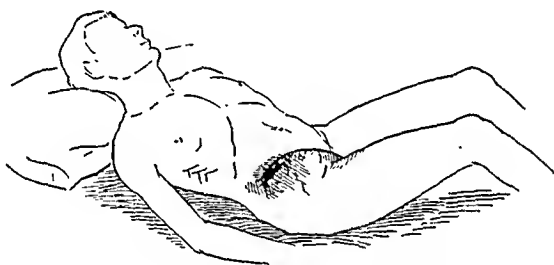


Fig. 1.—Sketch of the patient showing the enlarged right iliopectineal bursa, which fills in the pelvofemoral region; the hips are in flexion contracture.

of fluid, similar to that previously aspirated, gushed out. An elliptic portion of the roof of the wall of the tumor was resected for histologic study.

When the depths of the cavity were sponged dry, a smooth-walled, shining internal lining was exposed. In the lateral portion of the floor of the sac was a tiny valvelike flap overlying a 3 to 4 mm. opening which communicated with the hip joint. When the hip was passively moved, synovial fluid was seen to pass from the joint through the opening into the sac cavity.

The communicating tunnel and the adjacent portion of the bursal floor were resected, and the capsule was sutured tightly across the defect so as to obliterate the passage between the joint and the bursa. No attempt was made to resect the bursa, but its walls were everted and the medial fibers of the sartorius and iliopsoas muscles were anchored into the floor of the sac, furnishing a surface for adhesions and absorption. In a similar manner, the medial superficial fascial layers were anchored into the floor. The wound was then closed tightly by approximation of the superficial tissues and skin.

The histologic examination of the roof of the bursa showed a wall composed of dense fibrous tissue. The innermost lining layers were not differentiated into a definite synovial membrane but were arranged compactly in strata parallel to the surface and represented pressure layers (fig. 2). The next layers outward were

of the iliopectineal bursa (two and one half months after operation) showed effective obliteration of the cavity by scar tissue. There was no sign of reestablishment of the communication with the hip joint.

#### ANATOMY

All anatomists<sup>1</sup> describe the iliopectineal bursa, although some do not designate it specifically; iliopsoas bursa and bursa mucosa subiliaca are synonyms. The iliopectineal bursa is a constant structure and is said to be the largest bursa normally present. Kessel<sup>2</sup> definitely demonstrated its presence in the 25.75 mm. embryo. The iliopsoas muscle covers the anterior aspect of the capsular ligament of the psoas muscle and the joint capsule. The bursa is bounded anteriorly by the iliopsoas muscle; posteriorly, by the pectineal eminence and thin portion of the capsule of the hip joint; laterally, by the iliofemoral ligament; medially, by the cotyloid ligament; above by Poupart's ligament, and below, by the pubofemoral ligament.

The anterior crural nerve lies deeply between the fleshy and the tendinous portion of the iliopsoas muscle. The femoral artery, enclosed within the crural sheath, rests on the psoas magna muscle. The femoral vein, similarly enclosed, lies between the psoas magnus and the pectineus muscle (fig. 3).

In some cases the cavity of the iliopectineal bursa is directly continuous with that of the joint. The portion of the capsule between the iliofemoral (Y) and the pubofemoral (pubocapsular) ligament is very thin, and at this point the bursa is in intimate relation with the synovial membrane of the hip joint. Either the fibrous capsule or the synovial membrane or both may be defective, permitting communication between the two cavities. Kessel found such communication in 15 per cent of 535 adult anatomic specimens. Most of these are probably congenital, but trauma or friction may also tend to establish the communication.

The bursa, when pathologically enlarged, may extend far beyond its normal confines. Durville<sup>3</sup> stated that its upper limit does not extend above the inguinal ligament; Lund,<sup>4</sup> on the contrary, said that it might

1. Buchanan, A. M.: *Manual of Anatomy*, Chicago, W. T. Keener & Co., 1906, vol. 1, p. 438. Cunningham, D. J.: *Manual of Practical Anatomy*, ed. 8, revised and edited by Arthur Robinson, Baltimore, William Wood & Company, 1927, vol. 1, p. 278. Gray, Henry: *Anatomy of the Human Body*, ed. 21, revised by Warren H. Lewis, Philadelphia, Lea & Febiger, 1924, p. 468. Heisler, John C.: *Practical Anatomy*, ed. 2, Philadelphia, J. B. Lippincott Company, 1920, p. 224. Spalteholz, Werner: *Hand Atlas of Human Anatomy*, ed. 4, Philadelphia, J. B. Lippincott Company, 1923, vol. 2, p. 350.

2. Kessel, F.: Ueber die Bursa mucosa iliopectinea, ihre Entwicklung und ihre Kommunikation mit der Kapsel des Hüftgelenkes, *Morphol. Jahrb.* 58:413, 1927.

3. Durville, cited by Gatch and Green.<sup>9</sup>

4. Lund, F. B.: Iliopsoas Bursa, *Boston M. & S. J.* 147:345, 1902.



## REVIEW OF THE LITERATURE

The first description of the iliopectineal bursa appears in Vesalius' "De humani corporis fabrica" written in 1555, according to Kessel.<sup>2</sup> However, the first clinical case of iliopectineal bursitis was reported by Fricke<sup>7</sup> in 1834. During the next one hundred years thirty-five additional cases were added. Zuelzer<sup>8</sup> in 1899 wrote a classic on the subject of iliopsoas and trochanteric bursitis, reviewing fourteen cases gathered from the literature. In 1925 Gatch and Green<sup>9</sup> completed a survey of twenty-four cases, including one of their own. Finally, O'Connor,<sup>10</sup> in an excellent treatise, demonstrated the practical application of his

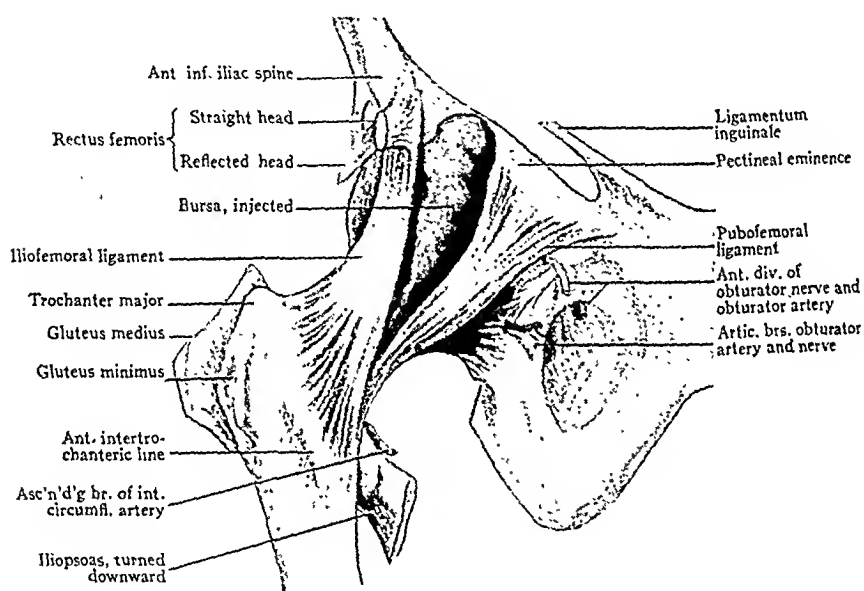


Fig. 4.—The injected iliopectineal bursa in relation to the ligamentous structures around the hip joint. (From Heisler, John C.: *Practical Anatomy*, ed. 2, Philadelphia, J. B. Lippincott Company, 1920, p. 224.)

experience by reporting thirty-three personal observations. The seven cases proved at operation lends credence to the accuracy of O'Connor's diagnoses in the remaining twenty-six instances.

7. Fricke, cited by O'Connor.<sup>10</sup>

8. Zuelzer, R.: *Die Schleimbeutel der Hüfte und deren Erkrankungen*, Deutsche Ztschr. f. Chir. 50:148, 1899.

9. Gatch, W. D., and Green, W. T.: *Cysts of the Ilio-Psoas Bursa*, Ann. Surg. 82:277, 1925.

10. O'Connor, D. S.: *Early Recognition of Iliopectineal Bursitis*, Surg., Gynec. & Obst. 57:674, 1933.

than in the articular synovia. Ardouin<sup>11</sup> in 1934 could find reports of only five cases in the inguinal region. Two sources of bursal bodies are possible: the bursal wall and the structures of the hip joint. The bursal wall may give rise to large bodies by a metaplastic process. Smaller bodies may result from degenerative changes in the bursal wall due to pressure. The affinity of necrotic tissue for lime salts is well known, and on this basis calcium may be precipitated in the bursal wall. In such cases the roentgenograms may possibly show an increased density in the outlines of the bursa.

When the calcified bodies originate from the structures of the hip joint, there is usually an antecedent trauma or osteo-arthritis, frequently both. Marginal lippings or exostotic spurs may chip off under stress of motion of the joint and be carried through a communicating aperture into the bursal sac, where they may enlarge by further deposition of calcium. As a rule, however, these foreign bodies are taken up by the fibrous tissue of the superficial layers of the bursal lining. This process is illustrated in my case report.

#### SYMPTOMS

The onset of symptoms in cases of iliopectineal bursitis due to trauma usually is acute and is characterized by rather severe pain in the groin. It is aggravated by movements of the hip, particularly extension, and is relieved by rest with the hip flexed. The involved area may show a fulness that is warm to the touch and tender to pressure. The gait is hampered by a limp. Applications of heat and rest, without weight bearing, usually alleviate the symptoms within two weeks. However, discomfort may persist if chronic bursitis develops.

In many instances iliopectineal bursitis is more insidious in its progress; it may follow some half-forgotten accident or unnoticed repeated minor occupational injury. Pain, which develops gradually, is first noticed after the fatigue of a day's labor. Later, efforts of rising from bed or from a chair evoke pain in the inguinal region. In addition to the direct pain caused by the bursitis, the patient may also complain of pain referred to the front of the knee as it radiates along the irritated femoral nerve. Timmermann<sup>12</sup> wrote that occasionally pain also radiates to the abdomen or the back. A limp impedes the gait because of the tendency to relax the psoas muscle by flexion of the hip. Ultimately, dragging of the extremity, limp, stumbling and weakness indicate atrophy and loss of muscle power of the psoas muscle, as O'Connor<sup>10</sup> observed.

11. Ardouin, G.: *L'osteocondromatose des synoviales et des bourses sereuses*, Rev. d'orthop. **21**:301, 1934.

12. Timmermann, H. W.: *Ueber die Bursitis iliopectinea*, Med. Klin. **29**:1172 (Aug. 25) 1933.

position of flexion, external rotation and abduction. In cases in which the condition is of longer standing, a tumor is palpable. A clear fluid may be aspirated, but in the rare case of suppurative or tuberculous bursitis cloudy material with inflammatory cells and positive bacterial cultures may be found.

When a swelling is present, other lesions must be differentiated. Hernia may be ruled out by its reducibility, the transmission of the cough wave and its infrequent impediment of the motion of the joint. Tuberculosis of the spine or sacro-iliac joint explains the usual psoas abscess (fig. 5); the pea-soup pus and its bacteriologic composition confirm the diagnosis. Sworn<sup>13</sup> reported three cases of acute psoas abscess, from which *Streptococcus haemolyticus*, *Staphylococcus aureus* and *Bacillus influenzae*, respectively, were isolated. Roentgenograms of the spine and pelvis were normal. However, the acute abscess, unlike the chronic tuberculous type, tracks outward into the sheath of the iliacus muscle and seldom passes deep to Poupart's ligament into the thigh. Malignant conditions develop insidiously, the patient declines rapidly, metastases may appear and biopsy is confirmatory. Dilatation of the femoral vein, aneurysm of the femoral artery and certain types of inguinal lymphadenopathy are less common.

In the absence of swelling, osteo-arthritis should be considered. Frequently, it is concomitant with bursitis and cannot be excluded. However, the greater age of the patient, the frequent involvement of several joints, the more lateral localization of pain over the neck of the femur (Duvernay<sup>14</sup>), the position of deformity in flexion, external rotation and adduction and the roentgenographic picture furnish points of differentiation. Primary psoitis occurs in childhood and in adolescence (Ingelrans and Minne<sup>15</sup> and Klages<sup>16</sup>) but is seen occasionally in later life. Trauma is followed by a limp and radiating pain in the leg. Lordosis in the lumbar region increases, the inguinal lymph nodes enlarge and fever develops. A flexion, abduction and external rotation contracture develops, as in iliopectineal bursitis, but the hip joint is free. The roentgenogram may show a definitely enlarged psoas shadow. Transitory synovitis of the hip joint is essentially a disease of childhood

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13. Sworn, B. R.: Acute Psoas Abscess, *Brit. M. J.* 2:6 (July 1) 1933.

14. Duvernay, cited by Burckhardt, Hans: Arthritis deformans und chronische Gelenkkrankheiten, in von Bruns, P.: *Neue deutsche Chirurgie*, Stuttgart, Ferdinand Enke, 1932, vol. 52, p. 362.

15. Ingelrans, P., and Minne, J.: Onze cas de psoïtis primitives observés chez des enfants et des adolescents, *Rev. d'orthop.* 20:577, 1933.

16. Klages, F.: Nichttuberkulose Psoaserkrankungen im Kindesalter, *Beitr. z. klin. Chir.* 158:171, 1933.

Treatment in the early stages is conservative. With the development of an enlarged, chronically irritated bursa, surgical treatment may be necessary. The method of obliteration is successful; it is suggested in preference to the more difficult procedure of total removal of the bursa.

An unusual case of iliopectineal bursitis is reported here.

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roentgen rays in order that the later appearance of new tumors in other locations may be prevented in a high percentage of cases. Application of this thesis to date has resulted in an increase in the percentage of complete regression of the primary tumors and a definite decrease in the appearance of recurrent new tumors in such cases.

Washburn <sup>46</sup> discussed the treatment of aniline tumor of the urinary bladder. In a group of 86 cases there were 9 deaths, a mortality of approximately 10 per cent. Twenty-four (28 per cent) of the patients had been treated too recently for a consideration of the end-results, and 53 men (62 per cent) were free from tumor. This is a creditable showing when one considers that there were 15 patients with extensive highly malignant lesions. It is to the credit of the dye industry that full responsibility has been accepted, that every facility has been provided for the discovery of early cases and that nothing has been left undone to restore the affected men to health.

Gay <sup>47</sup> stated that the disease produced by exposure to aniline affects the entire bladder and most frequently occurs in the lower half of the viscus above the level of the ureteral openings. The sequence of events is as follows: First, there is endothelial proliferation in focal subepithelial blood vessels. Occlusion of a vessel causes dilatation of afferent capillaries and edema of the surrounding tissue. Ectasia and proliferation of the capillaries form a mass of vessels; this mass may persist for months, or proliferation of the basal layer of the overlying epithelium may occur, with the formation of a tumor. The initial epithelial tumor may be of any degree of malignancy but tends to become more malignant with the passage of time. The sequence of vascular and epithelial lesions may be repeated indefinitely, and various stages of development as well as different grades of tumor may coexist.

Evans <sup>48</sup> stated, after making a study of cases of aniline tumor of the bladder, that an analysis of the literature fails to show conclusively either the carcinogenic agents or the mechanism of action in the production of such tumors. Analysis of a series of 83 cases of tumor of the bladder indicates that the tumors occur in persons who have been exposed to benzidine, betanaphthylamine, alphanaphthylamine and other nitro and amino compounds, while those exposed only to aniline have shown no tumors. The majority of the tumors appear after from six to twenty years of exposure. The average time is twelve years. The incidence of tumor is higher in persons from 40 to 60 years of age; an appreciable

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46. Washburn, V. D.: The Treatment of Anilin Tumors of the Urinary Bladder, *J. Urol.* **38**:232-242 (Aug.) 1937.

47. Gay, D. M.: Pathology of Anilin Tumor of the Bladder, *J. Urol.* **38**:221-231 (Aug.) 1937.

48. Evans, E. E.: Causative Agents and Protective Measures in the Anilin Tumor of the Bladder, *J. Urol.* **38**:212-215 (Aug.) 1937.

should be suspected. The surgical attack on a mesothelial tumor of the bladder differs in no way from that on an epithelial growth. Removal or destruction of the tumor in the most suitable manner adapted to the given case is the method of choice.

White and Gaines,<sup>51</sup> in an article on spindle cell sarcoma of the bladder, question whether all reported cases are true to type. They reported a case of sarcoma of the bladder in a man aged 38; after removal of the tumor, recurrence took place rapidly. Several sections of the growth were examined microscopically, and a diagnosis was made of transitional cell sarcoma with sarcoma-like areas. It was stated in the literature that of 69 patients with tumor of the bladder who were operated on, only 3 were considered cured; they were followed for a period of from three to twelve years. Liberal resection of the tumor-bearing wall of the bladder or complete cystectomy and urethral transplantation may result in cure in a case in which diagnosis is made early. However, only about 8 such cases have been recorded in the medical literature.

After a résumé and consideration of some practical points in the pathologic structure, symptoms and diagnosis of tumor of the bladder, Millin<sup>52</sup> discussed in some detail the treatment, emphasizing especially his method of endoscopic endothermic resection. The procedures available for the treatment of tumor of the bladder are:

1. High voltage roentgen treatment or distant radium treatment
2. Treatment by the urethral approach
  - (a) Diathermic coagulation with either the bipolar or the monopolar current
  - (b) Endothermic resection
  - (c) Introduction of radon seeds
  - (d) Aspiration of a bulky friable tumor (Born)
  - (e) Chemotherapy, consisting of the direct application of trichloroacetic acid (Joseph)
  - (f) A combination of two or more of the foregoing methods
3. Treatment by the suprapubic approach
  - (a) Partial cystectomy or segmental resection
  - (b) Total cystectomy with implantation of the ureters in the bowel or the skin
  - (c) Diathermic coagulation
  - (d) Endothermic resection
  - (e) Implantation of radium
  - (f) Application of actual cautery
  - (g) Low voltage roentgen therapy direct to the tumor with the Choaul applicator
  - (h) Permanent cystostomy
  - (i) A combination of two or more of the foregoing methods

51. White, E. W., and Gaines, R. B.: Spindle Cell Bladder Sarcoma, *Surg., Gynec. & Obst.* **65**:366-369 (Sept.) 1937.

52. Millin, Terence: Tumours of the Urinary Bladder with Description of a New Endoscopic Technique, *Brit. J. Surg.* **25**:145-171 (July) 1937.

On the basis of the results of treatment in 172 cases of vesical tumor, Millin concluded that the prognosis in cases of solitary papilloma is relatively good. With transurethral diathermic treatment, 65 per cent of the patients were free from recurrence at the end of three years. He considered the prognosis in cases of multiple papillomas to be grave. Only 4 patients were free from recurrences three years after diathermic destruction of multiple tumors.

The results following open operation for papillomas are disappointing. The outlook with endoscopic endothermic resection is much better.

Pfahler<sup>53</sup> stated that only about a fourth of the patients who have carcinoma of the bladder can be treated surgically without interference with the urethra or ureters; therefore, three fourths of the patients should be treated by irradiation. Treatment with highly filtered high voltage roentgen rays seems to accomplish more satisfactory results than other methods, especially in the inoperable group of tumors. This treatment involves less suffering and less interference with the daily habits of the patient than any other form of treatment. An insufficient number of patients have been treated by this method to make statistics of any value, but Pfahler estimated that one may expect disappearance of the tumor in from 30 to 50 per cent of cases.

After irradiation there is generally a cessation of hematuria at the end of three or four weeks. This does not indicate, however, that the disease has disappeared.

Cystitis is likely to be a complication before, during and after the roentgen therapy and must be dealt with just as cystitis would be treated under any other conditions. Anemia must be counteracted.

Pfahler aims to give the planned treatment within a month, which means from 20 to 25 treatments, but this number may have to be doubled or tripled. It is desirable to give as little treatment as will accomplish the results. The more accurately the disease is localized and the less its extent, the smaller will be the portals through which irradiation is given and the more one can conserve the normal tissues. On the other hand, if one confines treatment to too small an area, some remnant of the disease will be missed and recurrence will follow.

Mark<sup>54</sup> reported a case of endometriosis of the bladder in a patient whose chief complaints were hematuria, frequency, dysuria and disabling pain, these symptoms occurring with cyclic regularity and starting five months after hysterectomy. Because of the presence of endometriosis in the resected portion of the bladder, extending down to the perito-

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53. Pfahler, G. E.: *The Diagnosis and Treatment of Tumors of the Bladder by Means of Roentgen-Rays*, Surg., Gynec. & Obst. **64**:989-994 (June) 1937.

54. Mark, E. G.: *Endometriosis of the Bladder*, J. Urol. **37**:799-807 (June) 1937.

the bladder was begun with a row of sutures on the left side at the point of the greatest defect, the lateral walls being brought down medially to form a new floor. This line of interrupted chromic catgut sutures was continued until the opening of the bladder had been reduced to such size that it could be attached to the cut off apex of the prostate by a circular row of sutures. Two drains were placed in the wound, and the levator ani muscles were approximated with two sutures of chromic catgut. A no. 22 French catheter was left in the bladder.

Cystoscopy was performed at intervals of three months for the first two years after the operation and annually until five years had elapsed. There was no recurrence of the tumor and no history of further urinary difficulties.

Bumpus<sup>56</sup> reported a series of cases of tumor of the bladder from the Los Angeles County General Hospital. Destruction with diathermy was used in 77, in 34 through the urethra and in 43 by transvesical exposure. Eleven of the patients in the former group were living from three to five years after transurethral electrocoagulation—apparent cures in 33 per cent. These figures indicate how uncertain ultimate recovery is once a diagnosis of tumor of the bladder has been made. Unquestionably, the poor final results were due in no small measure to the failure of the patients to come for reexamination.

Of the latter group of 43 patients treated transvesically, 25 had tumors of the papillary type; 16 of these patients are known to be dead and 5 were alive over three years. Of the 18 patients with infiltrating tumors, 10 are known to be dead and but 1 was alive over three years. Fourteen patients, or 35 per cent, died as a result of the operative procedure. Since there were 6 patients alive from three to five years and 24 were known to be dead, there would seem to be approximately a 25 per cent possibility of relief by this method of treatment, which is apparently as high an incidence of possible cure as is to be expected by any method of treatment now known. In the series of cases in which transvesical exposure was used the ureteral orifice was included 29 times in the cautery destruction, and in 10 cases the involvement of the orifice was considered a decided factor in the unsatisfactory convalescence if not a direct cause of the patient's death.

Ward<sup>57</sup> reported 7 cases of tumor of the bladder in which cystectomy with transplantation of the ureter was successful. Previously reported statistics have been quite unfavorable. Zukerkandle collected reports

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56. Bumpus, H. C., Jr.: What We May Expect from Treatment of Bladder Tumors, *California & West. Med.* **47**:84-87 (Aug.) 1937.

57. Ward, Bernard: Total Cystectomy with Transplantation of the Ureters into the Pelvic Colon for Malignant Growth of the Urinary Bladder, Based on an Experience of Seven Successful Cases, *Proc. Roy. Soc. Med.* **30**:137-156 (Dec.) 1936.



In their summary the authors stated that they considered the following principles fundamental in obviating these dangers: a two stage operation for the ureteral transplantation; transplantation of the right ureter first and of the left, from two to four weeks later; a transperitoneal approach for ureterosigmoidostomy, no catheter or guides being left but the proximal end of the ureter being opened widely by a longitudinal slit; no drainage of the peritoneal cavity; removal of the bladder as soon as is practicable after the ureteral transplantation and the selection of patients preferably between 3 and 5 years of age.

With the technic of Ladd and Lanman, the actual transplantation of the ureter is done transperitoneally, as the dangers of peritonitis are considered far less than the dangers resulting from a rather blind extraperitoneal approach. In using the extraperitoneal approach it is impossible to be sure that the ureter lies in a straight line from the kidney and that it is free from all tension and kinking. The transperitoneal approach is especially important in transplanting the left ureter, which is done from two to four weeks after transplantation of the right ureter. Intravenous pyelograms in the cases in which this technic was used showed excellent results two years after operation, especially when compared with the results following the earlier types of this operation. There were no fatalities, and good control of the bowel was obtained in every case. Ladd and Lanman advised, however, not doing the operation until the child is from 3 to 5 years of age, as by that time the patient can cooperate in acquiring control over the rectum.

Intravenous pyelograms and determinations of the blood chemistry were made with reported cases. These were normal in enough cases to lead the authors to state that preoperative infection of the urinary tract is a rarity. Later infection of the urinary tract is more likely to occur with the so-called aseptic type of extraperitoneal operation than with an operation that strives to have the course of the ureter into the bowel as straight and as unobstructed as possible.

*Ulcer.*—Folsom and O'Brien<sup>59</sup> gave a preliminary report of their observations on 7 cases of Hunner ulcer in which absolute alcohol was injected into and about the ulcers. Gas anesthesia was used for all the patients. Injections were made with a long flexible needle through the McCarthy panendoscope. From 2 to 6 cc. was injected, 0.2 cc. being introduced at each puncture. These injections were distributed about and directly into the ulcer. After the treatment the patients spent from sixteen to twenty-four hours in bed and were then able to resume their regular activities.

According to Folsom and O'Brien, definite conclusions are not warranted on the basis of their brief report in which observations were

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59. Folsom, A. I., and O'Brien, H. A.: Transvesical Alcoholic Injection for Elusive Ulcer of the Bladder, *J. Urol.* **37**:808-814 (June) 1937.

and massage, (3) the use of an indwelling catheter and (4) early or prophylactic cystotomy.

With the first method, the bladder is allowed to distend without any local interference until overflow takes place, and eventually periodic reflex micturition develops. Although the deleterious effects of the over-distended bladder may have been overemphasized, this method is not recommended for universal adoption because of the possible effects on the musculature of the bladder and future function or on the function and structure of the kidneys; there is also a possibility of rupture of the bladder. The latter has been reported in a number of cases.

The second method consists in gentle but firm compression and massage of the distended bladder through the abdominal wall every four to six hours as soon as possible after injury, with the object of expressing its contents. It should be done early before distention becomes too marked and must be done carefully and skilfully because of the danger of rupturing the bladder. It should not be used when infection has set in.

When the indwelling urethral catheter is used, the bladder is irrigated daily; the catheter is changed twice a week and is removed when reflex micturition develops. This method is certain to produce infection, but if the bladder is kept empty it does not permit reflux and regurgitation to the upper part of the urinary tract. The disadvantages and dangers of this method are: intolerance to the catheter; periurethral infection; the expulsion or plugging of the catheter, permitting the infected bladder to become distended, and the constant supervision necessary to prevent these complications.

Thomson-Walker recommended the fourth method, or early drainage by the suprapubic route, to relieve the distended bladder until reflex urination develops. The objections to early cystotomy have been: (1) difficulty of obtaining a watertight wound, (2) possible interference with the development of automatic function and (3) cystitis, which is inevitable. These objections are groundless, because with ordinary skill the production of a watertight cystotomy wound offers no difficulties. For those to whom it does, the simplified trocar and catheter method of Mothersill and Morson is available.

Although cystitis is inevitable, infection without distention or increased intravesical pressure is not dangerous. Overdistention rather than drainage interferes with development of reflex micturition. Automatic emptying will follow no matter how long the bladder is drained. The suprapubic fistula at this stage heals without difficulty when the tube is removed. Therefore, although in some cases manual expression may be of value, the constant attention and skill necessary over long periods, the failure to empty the bladder completely in some cases and

entire ring being bound to the pubis by the pyramidalis muscle. Suture of the abdominal wall in three planes was somewhat difficult, owing to removal of the central flaps, but was successfully carried out. The first successful attempts at urination were accomplished three weeks later, under the synergistic action of the abdominal muscles and the diaphragm. A course of reeducation was instituted, with the result that at the end of six weeks the child could remain upright for five hours without urinating and could voluntarily void 100 cc. of urine. Continence was considered satisfactory from that time on. Rather extraordinary was the fact that fecal incontinence also practically disappeared, occurring only at the time when the effort to urinate was made. No vesico-ureteral reflux was present, and the capacity of the bladder was 120 cc.

The pure hypogastric Goebell-Stoeckel technic is much better from the point of view of asepsis than the vaginal approach but is a much more delicate operation. With separation of the tissues along the neck of the bladder, hemorrhage along the perivesical plexuses is inevitable, but the procedure was accomplished without evil consequences.

In discussing this case, Gouverneur stated that incontinence of urine in cases of spina bifida is of a special kind, owing to disturbance of endovesical sensibility. It is probable in the present case that a part of the curative action must be credited to the muscular ring formed around a neck of the bladder, followed later by a ring of perivesical sclerosis, but this mechanical action was not the whole, and perhaps not even the essential, correction. It is certain that in dilacerating the perivesical and pericervical nerve plexuses one exerts action on the vesical function, and it is probably in this manner that at the same time that Godard cured his patient of urinary incontinence action was exerted on the plexuses that control the anal function, so that the rectal incontinence also disappeared almost entirely. Amelioration of rectal incontinence is proof that the Goebell-Stoeckel operation finds its true usefulness in the fact that it removes the action of the sympathetic nervous system.

Hill, Barnes and Courville<sup>63</sup> stated that retention of urine with distention of the bladder is a fairly common complication of resection of the rectum for carcinoma. Cellules or small diverticula, ordinarily the result of long continued obstructive or paralytic distention, may appear within two weeks. Urinary retention may be transitory or may be present for days, weeks or even months or, occasionally, may be permanent. The extent and duration of vesical dysfunction depend on the character and extent of damage to the nervous elements.

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63. Hill, M. R.; Barnes, R. W., and Courville, C. B.: Vesical Dysfunction Following Abdominoperineal Resection for Carcinoma of the Rectum, *J. A. M. A.* **109**:1184-1188 (Oct. 9) 1937.

the presence of 15 cases on which there were sufficient data for study, and with the case reported by Kretschmer, the total is brought up to 16. The youngest patient was 4 years old, and the oldest was 69. The largest number of cases occurred in persons between the ages of 4 and 15 years. This verifies the statements which have been made that xanthine calculi occur more frequently in young subjects. The sex distribution shows that the males predominate.

Xanthine calculi reported in the literature have varied greatly in size. Langenbeck's specimen was the size of a hen's egg and weighed 338 grains (21,903 mg.). Jaillard's specimen was 2 inches (5 cm.) in length and weighed 350 grains (22,679 mg.); Fleming's specimen was a little larger than a garden pea; the multiple stones in Israel's case totaled 2,300 mg. in weight. The opinion has been expressed by some authors that xanthine calculi are found more frequently in the bladder than at other sites in the urinary tract. In none of the cases in this series was the stone found in the ureter. In 8 cases the stone was found in the bladder; in 3, in the kidney, and in 1, in the urethra. In 4 cases the location was not stated.

In Kretschmer's case roentgenographic examination gave evidence of stone in the bladder, and the review of the cases in the literature showed that positive roentgenographic findings were reported in 3 cases.

A small amount of xanthine is found constantly in the urine and may also occur in the feces with other purine bodies. Urinary calculi composed of xanthine do not seem to present clinical features distinct from other forms of urolithiasis.

Treatment of xanthine calculi does not present any special features distinct from the treatment of urinary lithiasis in general. At present the consensus seems to stress the importance of chemical examination of urinary calculi with the application of the knowledge gained to dietary measures, to prevent the formation of new concretions after operation. In cases of uric acid and xanthine calculi many authors advise a mixed diet with a preponderance of vegetables, fats and carbohydrates—a low protein intake of a purine-free nature.

*Rupture.*—Cahill<sup>66</sup> stated that the incidence of rupture of the bladder is increasing with the increase of automobile accidents. The usual cause of rupture is external traumatism to an overfilled bladder, not uncommonly seen in persons who use alcohol constantly. In an increasing proportion of cases rupture is associated with fracture of the pelvis. Occasionally rupture is secondary to medical manipulations. Intraperitoneal ruptures are more frequent than extraperitoneal ones. The symptoms and signs are shock, abdominal pain and tenderness, with a marked

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66. Cahill, G. F.: Rupture of Bladder and Urethra, *Am. J. Surg.* **36**:653-662 (June) 1937.

In the unmodified Maisonneuve procedure the two sections are not equal in depth, because they are made successively and not simultaneously. In Mihalovici's modification this inequality of the sections is overcome by making them with an instrument that has its two blades of unequal size. This produces two sections of equal depth, at the right and left of the midline. From this point on, the classic procedure is carried out, the conductor being replaced by a mandrin and a sound with a cut end of no. 20, 21 or 22 caliber being introduced. The patient retains this for three days, or in certain cases of callus or multiple strictures, from four to six days. As a rule, four days after the sound is removed dilation with bougies is begun; these are used daily, and the caliber is increased by one size each time. These are generally borne very well, and the maximum size is reached in two weeks. Mihalovici gives the name "period" to the precise interval of time elapsing between passage of the last *béniqué*, or bougie, and the moment when the stricture begins to contract again. This period varies for different strictures, but always remains invariable in one and the same person. The important thing is to establish this period with exactitude. With this end in view, Mihalovici proceeds as follows: After dilation has been done with a sound of the highest caliber, this sound is used again twice, at intervals of three days. After the second sitting, the patient returns in six days, then in twelve, twenty-four and forty-eight days and in two, three and four months and so on, and each time a sound of the caliber which was used last is passed. As soon as it is observed that the last sound is passed only with difficulty, the interval between sittings is diminished. Thus, if after three months sounds of smaller caliber are necessary, the period should be established at two and a half months. The patient must then present himself each time after this exact interval. Some patients have intervals of one, two or three months, but, more frequently, of four, five or six months and even up to one year. They then come to have the bougie passed once each time at the fixed term. Experience acquired during four years has taught that the period, once established, has never varied.

Patients are well satisfied with this improvement over old methods, and as a rule they come exactly on the day that marks their period. The only exceptions are patients with strictures in the anterior third of the penile urethra, who usually suffer rapid recurrence and to whom accordingly there is given a straight *béniqué* of suitable caliber which they pass for themselves at an interval of every two or three days.

If the stricture cannot be controlled or is complicated with fistulas, temporary or definitive cystostomy occasionally has its indications. In all other cases the dilated stricture can be maintained at the same caliber indefinitely.

Holtze<sup>71</sup> discussed the biologic action of the formation of urinary stone. The stability of urine in the urinary tract and its high power of dissolution are guaranteed by the low surface tension between the urine and the intact mucosa, by the presence of hydrotropic substances (urea and hippuric acid) and by content in stable colloids, which absorb comparatively insoluble substances and protect them from precipitation. Urinary calculi contain from 5 to 20 per cent of albumin as a nucleus. It is probable that primarily unstable, mucoid colloids mass together and become encrusted with salts. Urine penetrates in the albuminous mass, leaving the protecting colloids behind and causing the now unprotected, almost insoluble salts to precipitate. Stagnation of urine favors development of stones. With a few exceptions (cystinuria and hypercalcaemia) the concentration of stone-forming salts in the urine is unimportant. Elimination of calcareous salts through the kidneys is parallel with their concentration in the blood and can lead directly to the formation of stone. This occurs most commonly in cases of adenoma of the parathyroid gland.

Experimental and clinical data indicate that it is improbable that vitamin A is of importance in the prevention of stone in a mild climate. Unexplained are the following facts: regional, endemic occurrence of stone, a change in the frequency of stones in the same region over a certain period of time, the hereditary character of the condition, its preference for the male sex and its disappearance among children when they become adults.

Because of the results of experimental work on animals with diets deficient in vitamin A, Higgins<sup>72</sup> placed a selected group of patients who had urinary calculi on a dietary regimen aimed to meet the needs of the particular calculosis. Included in this group were: (1) those with bilateral renal calculi on whom operation was not advisable; (2) those with large renal calculus who ordinarily would require nephrectomy; (3) those with small calculus in the renal pelvis which was not producing obstruction, and (4) those with a small calculus in the calix which was not producing obstruction. Treatment was prescribed also when it was desirable (1) to prevent the formation of recurrent calculi, (2) to prevent the formation of calculi in patients who had passed stones at frequent intervals but in whom no calculus could be demonstrated roentgenographically, and (3) to prevent the formation of renal calculi in patients who had orthopedic problems.

It is important that the patient be hospitalized until he is thoroughly familiar with the intricacies of the dietary modifications and until the  $p_H$  of the urine is stabilized at the desired level. In cases of unilateral

71. Holtze, F.: *Biologische Grundlagen der Konkrementbildung*, Ztschr. f. Urol. **31**:334-338, 1937.

72. Higgins, C. C.: Present Status of Dietary Regimen in the Treatment of Urinary Calculi, Brit. J. Urol. **9**:36-46 (March) 1937.

the statement of Vorman and Welti, from the urologic clinic in Berne, that they were unable to find a single case in which avian tuberculosis was the cause of urogenital tuberculosis in man. Remete's examination was made on 42 patients and consisted of allergic cutaneous tests, culture and inoculations in guinea pigs and cockerels.

#### ANESTHESIA

Stockwell and Smith<sup>74</sup> related their experiences with pontocain as a spinal anesthetic in 1,000 urological operations. The technic for patients weighing 135 pounds (61 Kg.) or over is as follows:

No preliminary sedatives are given except to children. The authors prefer to administer sedatives, as needed, in the operating room.

For operations on the bladder, pelvis and lower extremities the injections were made at a level of third and fourth lumbar space as follows: for operations of one hour's duration, 1.5 cc. of pontocain hydrochloride, with the aspiration of 0.5 cc. of spinal fluid, and for operations of from one to three hours' duration, from 1.75 to 2 cc. of the drug, with no aspiration of spinal fluid. The average working dose is 1.75 cc. for operations of short duration and 2 cc. for those of long duration. The injection is made at the rate of 2 cc. per minute.

The dose for patients under 135 pounds is figured as 1 cc. of a 1 per cent solution for each 100 pounds (45 Kg.) of body weight and to this is added 0.25 cc. more for prolonged operations. The maximum dose is 2 cc.

Induction is easy and rapid, with an average time of six minutes for the appearance of surgical anesthesia. Perfect anesthesia was obtained in 959 patients and partial anesthesia in 40, of which a few required additional local anesthesia or a few inhalations of nitrous oxide.

Pontocain is slightly more toxic than procaine but when skilfully used no untoward reactions have occurred. Its distinct advantages are smooth onset, perfect anesthesia for two hours and possibly longer, complete absence of depression of the blood pressure, absence of disturbing gastro-intestinal reactions, smooth recovery and total absence of neurologic sequelae. The safety of any spinal anesthesia depends most on the skill and experience of the administrator.

#### HYPOCHLOREMIA AND UREMIA

Török and Babics<sup>75</sup> checked the sodium chloride content of blood and spinal fluid in 17 patients who had true uremia. They found the chlorides either within normal limits or lowered in the blood and spinal

74. Stockwell, A. L., and Smith, C. K.: Pontocaine Spinal Anesthesia in Urology, Surg., Gynec. & Obst. **65**:389-392 (Sept.) 1937.

75. Török, Alexander, and Babics, Anton: Beiträge zur Klinik der Hypochlorämie und der echten Urämie, Ztschr. f. Urol. **31**:243-249, 1937.

tract is complicated by chronic pyelonephritis with cicatricial changes in the pelves or calices, residual urine in the kidney or bladder, chronic prostatitis, stone and tumor, the chances of rendering the urine sterile are definitely reduced. Occasionally symptoms, such as nausea, evanescent microscopic hematuria or hyaline casts in the urine, may accompany the administration of mandelic acid. Some patients have experienced tinnitus and headaches, and rarely certain dermatologic reactions have been observed.

Braasch, in discussing Cook's paper, stated that the clinical evidence of renal irritation resulting from mandelic acid is indefinite. In 2 per cent of the cases red blood cells or a few hyaline casts were found in the urine. Gross hematuria was present in only 2 of the 500 cases. In no instance was there evidence of serious injury to normal kidneys following the administration of mandelic acid. In no case was an increase in the value for blood urea noted following the administration of the acid if the primary renal function was normal. In the presence of damaged kidneys, however, the use of mandelic acid may result in a mild temporary decrease in renal function. Braasch expressed the belief that use of this drug should be contraindicated if there is definite evidence of renal insufficiency.

Helmholz<sup>77</sup> conducted a series of experiments and made a preliminary report on the bactericidal power demonstrated in the urine of a patient who was taking sulfanilamide by mouth. He concluded that many of the organisms that are commonly found in cases of infection of the urinary tract fail to grow in the urine of a patient who has received an appreciable amount of sulfanilamide by mouth. Further reports on this will be forthcoming.

Buchtel and Cook<sup>78</sup> reported their experiences with sulfanilamide in the treatment of more than 200 patients who had infections in the urinary tract. This treatment is considered in general more dangerous than acidification of the urine and administration of mandelic acid, and the latter should therefore be used whenever it will prove effective. Mandelic acid is most successful in uncomplicated cases of bacillary infection and in infections attributable to *Streptococcus faecalis*.

Sulfanilamide appears to be a more potent antiseptic than mandelic acid and when used is effective in an alkaline urine and also at times in the presence of marked renal insufficiency.

Coccic infections do not respond as well to sulfanilamide as do bacillary infections; this is especially true of infections due to *Str. faecalis*. The authors present an analysis of results in the following conditions

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77. Helmholz, H. F.: The Bactericidal Power of the Urine After the Administration of Prontylin by Mouth, *Proc. Staff Meet., Mayo Clin.* 12:244-245 (April 21) 1937.

78. Buchtel, H. A., and Cook, E. N.: The Use of Sulfanilamide in Treatment of Urinary Infections, *Proc. Staff Meet., Mayo Clin.* 12:444-446 (July 14) 1937.



The authors' results from this dose of sulfanilamide have been so superior to those obtained by a constant small daily dose that it seems justified, in spite of the fact that 15 per cent of patients cannot take it. Some of these patients can start with a small dose and gradually work up to a larger one; others will obtain good results on a small daily dose; the remainder, about 10 per cent, cannot take the drug at all. It was early noticed that less sulfanilamide could be taken by an ambulatory patient than by one who is at rest in bed. Ordinarily, only the first two to three days will have to be spent in bed; after that, the dose can be reduced. Cook and Buchtel recommended this procedure when the patient is doing poorly.

Reactions are common and may prove very serious. Lassitude, dizziness and slight headache occur almost invariably. If these are relieved by rest, the dose need not be reduced. More severe reactions necessitate reduction of the dose or cessation of the drug. To continue large doses in the face of severe headache, fever, gastro-intestinal upsets, mild cyanosis, paresthesia or other reactions is inviting disaster. If any of these symptoms are severe or if cutaneous reactions occur, administration of the drug should be permanently stopped.

It is unnecessary to produce even the mildest reaction to obtain good results. As a general rule, patients taking the largest dose will show the best results. Men can take larger doses of sulfanilamide than women, and the young, more than the aged. With increasing experience, serious reactions become increasingly rare.

#### DIURETICS

Keith<sup>79</sup> stated that the diuretic action of mercurial compounds depends on the available amount of mercury present. Organic mercurial compounds produce the most marked immediate diuresis. The action is chiefly on the kidneys. Diuresis which follows the administration of mercurial compounds is usually more satisfactory than that which follows the use of digitalis or caffeine compounds, even in cases of cardiac disease. The usual procedure is to inject intravenously 0.5 cc. of a given organic compound as an initial trial dose. If no toxic effects are evident, 2 cc. is injected every three or four days as long as there is distinct diuretic response.

Of the acid-producing salts, ammonium nitrate has the most marked diuretic effect and causes less digestive disturbance. The diuretic effects of the xanthine derivatives are not so great, so rapid or so uniform as are the effects of organic mercurial compounds. The combined use of diuretics has a distinct place in present day treatment of dropsy. The

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79. Keith, N. M.: The Action and Use of Diuretics with Especial Reference to Mercurial Compounds, *J. A. M. A.* **107**:2047-2051 (Dec. 19) 1936.

clinical significance. In fact, complete visualization of the renal calices is not obtained in most cases. In some cases the filling defect may be visible in the first urogram but may disappear in subsequent urograms, or vice versa. In many excretory urograms peristalsis is so active that visualization of the renal calices or pelvis may be extremely fragmentary, which in some cases may be explained by some form of imbalance in sympathetic innervation. Further difficulty in interpretation may be caused by overlying intestinal shadows, which often simulate filling defects in the renal pelvis. That these various apparent filling defects are frequently without anatomic basis is shown by their subsequent disappearance in a retrograde urogram. On the other hand, filling defects observed in the excretory urogram, when confined to the renal pelvis or to one or two renal calices and when they persist in the retrograde urogram, may be the only urographic evidence of an organic lesion and should be regarded as important evidence. Fragmentary visualization of the renal calices in the excretory urogram may disguise an actual filling defect, and if a neoplasm is suspected, a retrograde urogram should always be made.

Filling defects of organic origin which involve the renal pelvis, renal calices and the ureter are caused by a great variety of conditions, including tumor, blood clots, lithiasis, cicatricial changes, congenital deformity, postoperative deformity, granulomas, pyelo-ureteritis cystica, air bubbles, reflex spasm and tuberculosis.

Braasch and McDaniel discussed renal tumor as a common cause of filling defects in the outline of the renal pelvis and the renal calices, which may be visualized in the urogram. Although a cortical tumor usually affects the outline of the calices more than that of the renal pelvis, it may invade the pelvic lumen to a variable degree and occasionally will obliterate it. A filling defect caused by papillary epithelioma of the renal pelvis is usually confined to the renal pelvis itself, and it is often accompanied by a variable degree of pyelectasis, which involves all the calices as well as the pelvis.

Clotted blood is a common cause of a filling defect in the renal pelvis or in the ureter. This may be confined to a small portion of the pelvis or ureter, or it may obliterate their lumen entirely. When blood clots become large and organized and cause persistent urinary obstruction, temporary dilatation of the pelvis and calices may result. Blood clots usually will cause an irregular filling defect, and the shadow produced by these clots often contains areas of variable density, which suggest vacuoles. Such filling defects may be confused easily with those caused by papillary epithelioma of the renal pelvis, which sometimes causes a similar deformity. In order to exclude the possibility that filling defects observed in the urogram might be the result of recent hematuria, urogra-

## FEVER THERAPY

Desjardins, Popp and Stuhler<sup>83</sup> reviewed the results obtained by fever therapy in cases of gonococcic infection of the urethra, epididymis, prostate gland, uterus, fallopian tubes and articulations from the time this form of treatment was started until July 1, 1936. During this interval various changes in the technic of treatment have been made. By these improvements in treatment, cure was effected in 92 per cent of the cases that were reported in 1936. Between Dec. 1, 1933, and July 1, 1936, 210 patients suffering from acute or chronic gonorrheal infection were treated with fever therapy. Of this number, 41 did not complete their treatment, or treatment had to be abandoned for various reasons. This group of patients was excluded from consideration. Of the 169 patients who had a complete course of treatment, 152, or 90 per cent, were cured and have not had any further physical difficulties caused by the gonococcus. Seventeen patients, or 10 per cent, were not completely cured, but their condition was improved in varying degrees. Details regarding the technic of treatment, the type of patients subjected to treatment, the criteria for cure, the factors of importance in reducing the risk of treatment to a minimum and the symptoms resulting from fever therapy are discussed.

According to the authors, it would be contrary to fact to say that fever therapy is entirely devoid of danger. At the time of their report, 516 patients had been treated with fever therapy for various conditions, and these patients had received approximately 2,580 sessions of treatment. Of this number, 1 patient died under treatment.

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83. Desjardins, A. U.; Popp, W. C., and Stuhler, L. G.: Fever Therapy for Gonococcic Infection, *M. Clin. North America* 21:885-891 (May) 1937.

complete description of the syndrome. Hamann<sup>3</sup> in 1907 reported 3 cases, the patients being respectively 13, 5 and 2 years of age, in which suppuration started primarily in the iliac glands, giving the typical picture of fever, flexed thigh and mass in the iliac fossa. Huggins<sup>4</sup> reviewed the literature up to 1911 on suppuration in the retroperitoneal space. Of the 8 cases he reported, 2 were instances of the iliac variety.

The syndrome of iliac adenitis is apparently well known in South America. From Argentina, Rivarola<sup>5</sup> in 1924 presented a clear and accurate description of the disease. Lugones<sup>6</sup> in 1926 observed 3 cases in which the condition occurred in children and was metastatic following bronchopneumonia. Coutts<sup>7</sup> in 1927, from Chile, reported 4 cases, in all of which the disease was traceable to preceding infection in the urethra, the prostate or the rectum. Bailey<sup>8</sup> in 1930 published reports of 7 cases, and in 1935 he had observed 5 more. Hyman<sup>9</sup> in 1930 was able to collect data on 21 patients with the condition who had been admitted to Mount Sinai Hospital, New York. Both Bailey<sup>8</sup> and Hyman<sup>9</sup> commented on the scarcity of publications on this subject. Largos García<sup>10</sup> in 1931 reviewed the South American literature, presented 38 cases of his own and admirably summarized the clinical picture. Barbarousse and del Campo<sup>11</sup> in 1933 published in detail the reports of 10 cases from Uruguay. Bose<sup>12</sup> in 1934 recorded 2 cases in which the condition simulated appendicitis. To the records of the 92 cases just mentioned I add the 18 following.

3. Hamann, C. A.: Suppuration in the Retroperitoneal Glands, *Cleveland M. J.* **6**:399, 1907.

4. Huggins, R. H.: Suppuration in the Retroperitoneal Space, *Surg., Gynec. & Obst.* **12**:276 (Feb.) 1911.

5. Rivarola, R. A.: Adenitis iliaca agudas, *Bol. y trab. de la Soc. de cir. de Buenos Aires* **8**:195, 1924.

6. Lugones, C.: Adenitis agudas de los ganglios iliacos, *Rev. méd. latino-am.* **11**:124 (Jan.) 1926.

7. Coutts, W. E.: Acute Inflammation of Deep Iliac Lymph Nodes, *Rev. Soc. urol. de Chile* **9**:268 (Nov.) 1926.

8. Bailey, H.: Suppurating Deep Iliac Glands, *Practitioner* **124**:223 (Feb.) 1930.

9. Hyman, A.: Suppurative Retroperitoneal Pelvic Lymphadenitis, *Ann. Surg.* **91**:718 (May) 1930.

10. Largos García, A.: La adenitis iliaca aguda, *Semana méd.* **2**:1160 (Oct. 8) 1931.

11. Del Campo, R. M., and Barbarousse, C. M.: Las adenitis iliaca agudas en el niño, *Arch. de pediat. d. Uruguay* **4**:43 (Feb.) 1933.

12. Bose, M.: Lymphadenitis of the Retroperitoneal Glands Simulating Appendicitis, *Indian M. Gaz.* **69**:579 (Oct.) 1934.

of the wall of the tumor removed for biopsy was described by the pathologist as follows: There was homogeneous grayish white tissue which showed numerous closely packed, medium-sized polygonal cells with pale, vacuolated, acidophilic cytoplasm and prominent oval nuclei. Local hemorrhage and numerous foci of infiltration by polymorphonuclear leukocytes were present. The diagnosis was chronic inflammatory changes (fig. 2). With drainage of the abscess convalescence was rapid, and the boy was discharged twenty days after admission.

CASE 4.—L. A., a girl aged 8 years, was admitted to the hospital in January 1935, complaining of pain in the right lower quadrant of the abdomen, fever and inability to extend the right thigh during the past five days. She had had a chronic vaginal discharge since infancy. Physical examination disclosed a soft abdomen in which could be felt a globular hard, fixed, tender mass, 6 cm. in

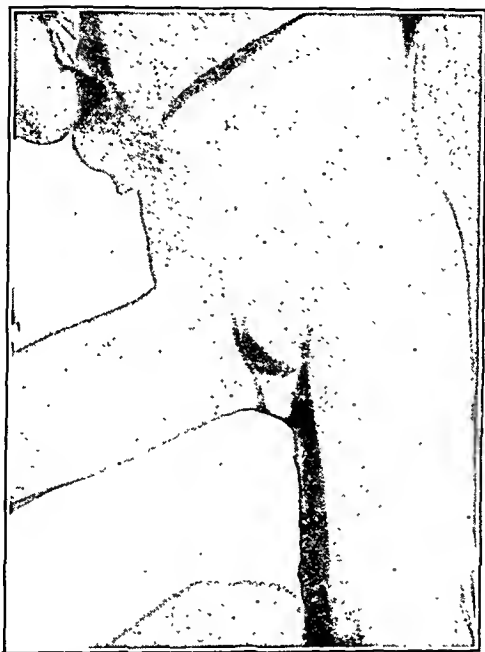


Fig. 1 (case 3).—Photograph illustrating spasm of the psoas muscle with flexion of the right thigh. The tumor is visible in the right iliac fossa (upper margin outlined with mercurochrome).

diameter, occupying the right iliac fossa. The right thigh was flexed on the abdomen. A leukocyte count of 21,900, an erythrocyte count of 3,200,000 (indicating secondary anemia) and a hemoglobin content of 59 per cent were observed. A mixed bacterial flora was present in the vaginal smear. No improvement was obtained with local heat. At operation an incision was made above and parallel to the inguinal ligament. A small abscess was found in the iliac glands, and was drained. *Staph. aureus haemolyticus* was grown from the pus. Recovery was uneventful.

CASE 5.—S. O., a boy aged 4 years, entered the hospital in September 1925. He had had a chronic infection of the upper respiratory tract for two months and pain in the right lower quadrant of the abdomen for two weeks. He had fever and had vomited. Physical examination revealed a feverish sick child with the

*Thirteen Additional Cases of Acute Iliac Adenitis*

Case No.	Age, Sex	Symptoms	Duration	Predisposing Cause	Clinical Findings	Laboratory Data	Operation	Bacteriologic Findings	Result
6	10 M	Pain in left lower quadrant; temperature 103 F.	12 days	Pyogenic infection of skin of leg	Psoas muscle spasm on left side; mass in left iliac fossa	R.B.C. 3,500,000; hemoglobin 50%; W.B.C. 12,000; whip ova	Drainage of retro-peritoneal iliac abscess	Culture not made	Discharged well in 21 days
7	2 F	Pain in abdomen; temperature 102 F.	11 days	Old cutaneous infection on right knee	Round tender mass in right iliac fossa; psoas muscle spasm	R.B.C. 3,300,000; hemoglobin 60%; W.B.C. 15,050; ascaris ova	Drainage of retro-peritoneal abscess 3 cm. in diameter in iliac fossa	Staph. aureus haemolyticus	Recovery in 35 days
8	3 F	Pain in left lower quadrant of abdomen; temperature 101 F.	14 days	Not known	Hard tumor in left iliac fossa; psoas muscle spasm on left side	R.B.C. 3,200,000; hemoglobin 50%; W.B.C. 13,800; Kahn test negative	None (medical treatment)	.....	Recovery in 24 days; disappearance of mass
9	21 M	Pain in left lower quadrant of abdomen; temperature 101 F.	30 days	Cutaneous infection on left knee	Psoas muscle spasm on left side; mass in left iliac fossa	R.B.C. 2,500,000; hemoglobin 45%; W.B.C. 22,000	Incision and drainage of large iliac abscess	Staph. aureus haemolyticus	Recovery in 18 days
10	5 F	Pain in right side; temperature 102 F.; anorexia; vomiting	7 days	Not known	Mass in right lower quadrant; psoas muscle spasm	Hemoglobin 75%; hook ova in stools	Drainage of small abscess in iliac glands	Culture not made	Recovery in 14 days
11	16 M	Temperature 104 F.; abdominal pain	10 days	Not known	Psoas muscle spasm; mass in right iliac fossa	W.B.C. 31,800	Drainage of iliac abscess	Culture not made	Recovery in 29 days
12	21½ M	Pain in abdomen; temperature 101 F.; inability to extend left thigh	21 days	Trauma; fall with blow on left buttock	Tumor in left lower quadrant of abdomen; psoas muscle spasm on left side	R.B.C. 4,100,000; hemoglobin 70%; W.B.C. 9,400	Drainage of iliac abscess; 100 cc. thick pus	No growth	Uneventful recovery

psoas muscle and the external iliac artery. The lowest gland of this chain, located behind the crural arch, is usually of fair size and is called the retrocrural gland (fig. 3). It is the gland most often involved. The majority of lymphatics which eventually terminate in the external iliac chain end in this gland. It receives efferent lymphatics from the superficial and deep inguinal glands draining the buttocks, the perineum and the lower extremity, and some deep lymphatics from the subumbilical portion of the abdominal wall (Poirier, Cuneo and Delamere<sup>13</sup>).

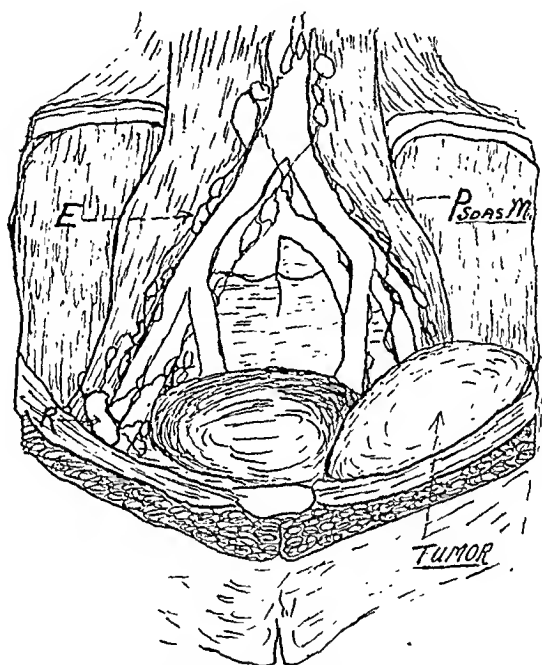


Fig 3.—A schematic representation of the pelvic lymphatic glands and the usual location of the inflammatory tumor. *E* indicates external iliac lymph glands, and *R*, the retrocrural gland.

Predominantly, iliac adenitis is a disease of childhood, especially in Latin and tropical countries, where the children of the poor wear no shoes and cutaneous infections are common. In the 92 cases mentioned in the literature, 76 patients were children or young adults. The average age in my own series was 9 years. The disease is more common in boys than in girls, the proportion being 63 boys to 29 girls in the cases reviewed and 13 boys to 5 girls in my own series. Undoubtedly the reason for this is that trauma and infection are more common

13. Poirier, P.; Cuneo, B., and Delamere, G.: *The Lymphatics*, Chicago, W. T. Keener Co., 1904.

## TREATMENT

Conservative treatment is recommended at first. It consists of continuous hot or cold fomentations applied locally over the mass, correction of anemia, a high caloric and high vitamin diet and general nursing care. Of the 18 patients in this series of cases, 5 were cured by this regimen. There were 10 patients who did not improve with medical treatment and who were operated on. In three instances a mistaken diagnosis of acute appendicitis was made prior to operation.

At operation an incision which offers an extraperitoneal approach is made over the mass parallel to and above the inguinal ligament. The thick-walled sarcomatoid tumor which is found is incised, and the cavity of the abscess is drained.

Cultures of material from 7 of the 12 patients operated on produced hemolytic staphylococci. It is not understood why inflammation in the retroperitoneal glands produces the hypertrophic tumor so often encountered (fig. 3). Lugones commented on the sarcoma-like appearance of the abscess. Figure 2 shows a section of the wall of the abscess in case 3, which at operation measured 3 cm. in thickness.

When incorrectly diagnosed or neglected, the abscess may point in Scarpa's triangle, at the umbilicus, into the pelvis or into the peritoneal cavity, with fatal results. Rivarola<sup>5</sup> reported a case in which the abscess eroded the iliac artery. With correct diagnosis the prognosis is good. No deaths occurred in the 18 cases of this report. There were 8 deaths among the 92 cases reported in the literature, a mortality rate of 6.7 per cent.

## SUMMARY

Acute iliac adenitis is an uncommon clinical entity, frequently incorrectly diagnosed. It occurs usually in children and is characterized by pain in the iliac fossa, fever and spasm of the psoas muscle. A hard, tender, fixed tumor is palpable above the inguinal ligament. At operation pus is encountered deep in the mass. With adequate drainage recovery is the rule.

The scanty literature on the subject is reviewed, and 18 additional cases are reported.



of the condition. Some authors have stated that the cause is acute appendicitis and that removal of the appendix is necessary.

As will be shown later, the diagnosis of mesenteric adenitis is not an elusive mystery, but is rather simple. It is, however, of the utmost importance to bear in mind the essentials of the anatomy and physiology of the mesentery and of the glands situated between its leaves.

In this series were 140 cases which came to my personal attention. Of the first 100, in every alternate case exploration was made to corroborate the diagnosis.

The mesentery of the small intestine begins at the left side of the second lumbar vertebra near the duodenojejunal attachment and runs diagonally downward and to the right, ending near the right sacroiliac articulation. It is about 15 cm. long at its root, but after spreading out into the shape of a fan it attains a length of 5 meters at its intestinal attachment and is therefore freely movable throughout, except at the ends. The mesentery of the terminal portion of the ileum differs in important details from the rest. A clear understanding of the anatomic arrangement of this area will make the diagnosis simpler. The last 6 cm. of the mesentery of the ileum is free from glands. Its fibers converge from left to right, and no vessels traverse this space. It is often called the avascular space of Treves. On the posterior surface of this fold is a space called the ileocecal fossa; an occasional small blood vessel is seen traversing it from left to right (fig. 1).

The lymphatic drainage of the intestines is accomplished by means of two sets of vessels. One set originates in the mucosa and the submucosa; the other takes its origin in the muscularis and the subserosa. The former is in close association with Meisner's plexus, and the latter with Auerbach's plexus. The submucosal plexuses receive the efferent lymphatics from the intestinal villi draining the lumen of the intestines; those coming from the muscularis and subserosa are fewer and drain the intestinal wall. The efferent lymphatics of the mucosa run directly into the mesenteric leaves, emerging at their attachment to the intestines; those coming from the intestinal wall often run some little distance before joining the more voluminous trunks, with which they enter the mesentery. These combined channels form the collective trunks known as Oselli's chylifers (collectives of the jejunum and ileum). Some authors have described three distinct sets of glands in the mesentery grouped along the avascular arcades. Rouviere, in his extensive studies, failed to find the lymphatic glands in distinct groups. My experiments bear out his observations.

The following experiments were made on living subjects in the course of laparotomies on both animals and human beings. With a 28 gage needle (this size being used to avoid too much pressure), a 1

cecal glands. A number of lymphatic glands are found in the ileocecal angle that drain the appendix, the cecum and the lowermost small segment of the ileum. These drain along the mesenteric artery, running diagonally upward and emptying into the chain near the third portion of the duodenum. The glands of the rest of the large intestines are similar to those of the jejunum and the ileum in their arrangement, but are not so numerous (fig. 2).

The physiology of the lymphatics of the small intestines is well known. The retrograde flow described by Braithwaite has not been corroborated. His experiments were carried out on cadavers, and the

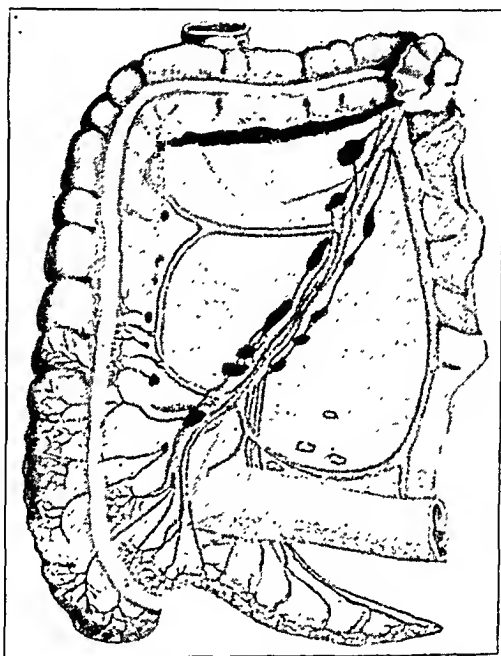


Fig. 2.—Lymphatics of the cecum and appendix. The collected lymph takes the direction of the superior mesenteric artery and empties into the area of the third portion of the duodenum. (Gray, Henry: *Anatomy of the Human Body*, edited by W. H. Lewis, Philadelphia, Lea & Febiger, 1930.)

results cannot be substantiated by observations on living subjects. I failed to duplicate his experiments on living animals. The intestinal glands empty into the thoracic duct and thence into the general circulation. The reverse process is physiologically not possible.

The pain of mesenteric adenitis is not easily explained, though there is some knowledge of the mesenteric response to external stimuli. While it is true that the intestines are insensitive to such stimuli as cutting, pinching and burning, the ganglionic plexuses of Meisner and Auerbach may be responsive to some forms of stimuli that cannot be

continued inflammation or to repeated attacks of mesenteric adenitis is probably correct. Felsen suggested that the cause factor of mesenteric adenitis may be a form of bacillary dysentery. In this series no thorough study was made, but of 30 studied cases in only 3 was there positive agglutination. The general impression that diarrhea accompanies enteritis is erroneous, as was pointed out by Felsen in his studies of bacillary dysentery.

When the abdomen is explored a few days after the onset of the disease, the acute inflammation of the intestines may have subsided. There remains, however, some thickening of the wall, and the color is often seen to be a light pink. Perhaps in some cases the toxins enter the lymphatic channel directly from the mucosa without affecting the wall of the intestines.

The frequency of mesenteric adenitis cannot be estimated with any approach to accuracy. For 18 of 100 consecutive children and adolescent patients admitted to my service in the wards with a diagnosis of acute or subacute appendicitis, a diagnosis of mesenteric adenitis was made after examination and proved correct at operation. Still, quoted by MacFadden, found that 59 per cent of children on whom autopsy was performed had enlarged mesenteric glands. This disease is prevalent in children and adolescents and is rare in adults. I have observed only 1 adult patient, a man 30 years of age. I failed to make a diagnosis, his being one of the early cases. The youngest patient in whom the disease was recognized was 3 years old. The average age of the patients in this series was 12.1 years; 58 per cent were girls and 42 per cent boys.

That the diagnosis of mesenteric adenitis is not difficult may be gathered from the fact that my house surgeons have learned to recognize this condition with remarkable frequency. In this series we had 2 cases in which the condition was not diagnosed correctly, the case of the 30 year old man, just mentioned, and the case of a child acutely ill, with a temperature of 105 F., in which we made the diagnosis of toxemia due to streptococcic infection of the throat, with inflammation of the intestines and the mesenteric glands. A note on the chart mentioned the possibility of appendicitis but added that the patient was too ill to be operated on. After thirty hours, when the temperature was much lower an exploratory laparotomy was performed and acute appendicitis was found. The whole intestinal tract was highly inflamed, the intestinal wall much thickened and the glands in the mesentery enlarged. The patient recovered.

Nonspecific mesenteric adenitis can be roughly separated into three types. The first is the least common and in this series only 8 cases occurred, all the patients being between 6 and 12 years of age. A sudden onset within twenty-four hours, with a temperature ranging

part of the abdomen, but the sudden removal of the palpating hand from the left lower quadrant does not cause rebound tenderness on the right side. Tenderness is found over a small area to the right of

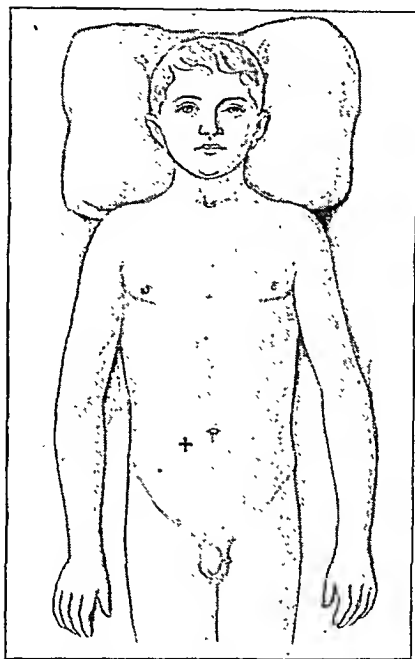


Fig. 3.—The tender point in mesenteric adenitis is at a higher level than in appendicitis and is internal to McBurney's area.

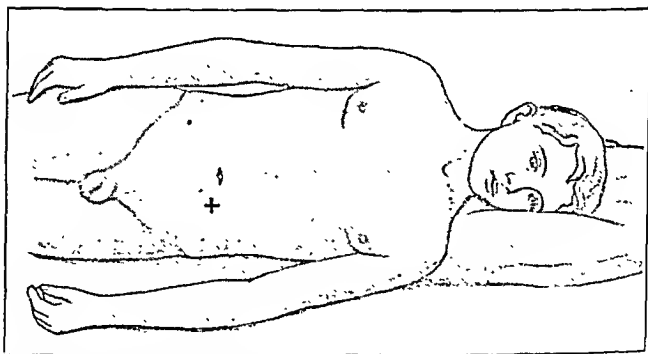


Fig. 4.—When the patient is turned to and allowed to rest on the left side, the tender area is shifted to the left and is absent on the right, as indicated by the cross.

the umbilicus, but much higher than McBurney's point. The tender area may extend even above the umbilicus on the right side. The left side at this time is free from tenderness. The patient is then turned on the left side and allowed to remain in this position for thirty seconds

onset, the small intestine may be found normal in appearance, but thickened, and the mesentery near the intestines free from glandular enlargements. Lower, nearing the spine, the glands are present in small groups and are lighter in color (fig. 5 *B*). They sometimes attain the size of a small walnut. In cases of recurrent involvement the glands are found near the spinal attachment and are never so large. These are much harder than in the early stages. This condition may persist for a long time. In some cases when operation is delayed one or more weeks the ileum is found normal in appearance. It is perhaps possible



Fig. 6.—Various stages of mesenteric hyperplasia in nonpyogenic adenitis of the mesentery.

that absorption of the toxic agent takes place directly into the mesentery lymphatics from the mucosa without involving the muscularis and the serosa.

The third type gives the same history as the second, but with this type examination of the abdomen discloses that whereas the tenderness can be shifted from right to left with change of position there persists a tenderness over the cecum. This type cannot always be differentiated from a pathologic process which involves the appendix. The findings at operation are somewhat as follows: The small intestine, particularly the lower ileum, is moderately inflamed, the cecum more so.

The pathologic report of the appendixes and glands removed during laparotomies in these cases is of special interest. From all patients laparotomized the appendix was removed, and in 20 cases one or more glands were removed for study. Felsen studied some of these appendixes by injecting the lumen with barium sulfate and correlating his findings with the histologic evidences, using a suitable number of normal controls. He found the mucosa intact, and sections failed to show actual pathologic conditions. Congestion was present in a small number of the appendixes. All glands removed proved to be sterile on culture; sections showed cellular infiltration, as can be seen in figs. 5 A, 6 and 7.

For the patients on whom operation had not been performed and who were under observation in the hospital for five days or more, the following routine was adopted: All solid food was interdicted for at least four days. During this period fruit juices were given freely and boiled milk in small quantities. Liquid petrolatum was given to overcome possible constipation, but all irritating cathartics were avoided.

The patients operated on had an uneventful convalescence.

As most of the patients were in the wards a thorough follow-up was impossible. Only 50 patients (25 of whom had been operated on) were observed from one to two years after either observation or operation. Both sets of patients had repeated mild attacks of abdominal pain. An interesting observation was that private patients not institutionalized continued to have severer attacks of pain than those kept under observation in the hospitals, though the latter came from much poorer surroundings.

#### CONCLUSIONS

1. Mesenteric adenitis is much more common than is generally recognized.
2. A diagnosis is possible in a majority of cases.
3. Mesenteric adenitis is not necessarily an accompaniment of an infection of the upper respiratory tract.

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# DISTRIBUTION AND EXCRETION OF WATER AND CHLORIDES AFTER MASSIVE SALINE INFUSIONS

AN EXPERIMENTAL STUDY

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Massive intravenous infusion has become an accepted therapeutic measure of wide application among practitioners of medicine and surgery, and present trends in medical practice seem to indicate even more extensive use of the method in the future. Nevertheless, comparatively little is definitely known about the physiologic responses of the body to the direct artificial addition of solutions of inorganic substances to the circulation. This is because the procedure has developed primarily at the bedside rather than in the experimental laboratory. Moreover, as ordinarily practiced, it has proved almost completely devoid of danger to life.

Because of the simplicity of the common vehicles of infusion—watery solutions of sodium chloride and dextrose usually—the consideration of intermediate metabolism has not seemed to most practitioners a serious issue, and the attention of experimentalists has turned, rather, to such matters as the causation and prophylaxis of the postinfusion reaction. It is true that attention has been paid to the assimilation and elimination of dextrose when used in infusions, and some consideration has been given to the factor of hypertonicity. By and large, however, the fundamental proposition that parenterally administered fluids are the physiologic equivalents of the same fluids administered by mouth has never been subjected to thorough experimental investigation.

The experiments to be reported in this communication were originally designed to determine the maximum rate of infusion compatible with survival and the lethal dose of essentially isotonic solutions of sodium chloride. It was moreover proposed to discover the cause of death after such lethal infusions and to trace the intermediate assimilation, *trans-*

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for the cat. Therefore, we have arbitrarily selected the strength of 1 per cent as being sufficiently close to the proper value for practical purposes. This figure is nevertheless not so exactly the proper value as to make it appear that we consider isotonicity actually critical.

In most of the acute experiments tracheal cannulation was performed, and blood pressure and respiration were continuously recorded on a long paper kymograph. The blood pressure was taken by direct cannulation of the common carotid artery and the respiration recorded from the tracheal cannula through a rubber tube connecting with a sensitive tambour.

#### PRELIMINARY EXPERIMENTS TO DETERMINE THE "LETHAL DOSE" OF SOLUTIONS OF SODIUM CHLORIDE

Our recorded tabulation (table 1) includes results from 10 cats. A considerably larger number of animals was actually used, omissions in

TABLE 1.—*Rates of Injection and Total Amounts of Sodium Chloride and Water in Lethal Doses of Saline Solutions Administered Intravenously\**

Cat Number	Strength of Sodium Chloride Solution, %	Weight of Animal in Kg.	Rate of Injection in Ce. per Kg. of Body Weight per Min.	Total Volume in Ce. per Kg. of Body Weight	Total Sodium Chloride in Ce. per Kg. of Body Weight per Min.
2A	1	1.53	7.71	503	5.03
9A	1	2.95	6.68	517	5.17
10A	1	2.77	4.04	639	6.39
11A	1	2.88	4.44	446	4.46
3A	2	2.50	5.68	320	6.41
4A	2	2.78	4.53	241	4.82
7A	2	2.90	3.93	196	3.93
8A	2	3.45	3.24	362	7.24
6A	5	2.40	1.66	170	8.50
5A	10	1.76	4.23	55	5.51

\* The injections were continued at a constant rate until death occurred.

the final record being made in order to avoid unnecessary compounding of evidence. Four cats received a 1 per cent solution of sodium chloride, 4 others a 2 per cent solution and the 2 remaining a 5 per cent and a 10 per cent solution, respectively.

The death of the animals in all cases was obviously due to the injection of sodium chloride in water, and the fatal dose is a matter of record. It is not, however, strictly accurate to speak of this as the lethal dose in the same sense as that in which the term is applied to intrinsically toxic substances. Both water and sodium chloride are, of course, normal constituents of the blood stream, and they become toxic only fortuitously, when their relative concentrations are grossly disturbed. The data for the first and the last animal of the preceding table clearly exemplify this statement, since both received approximately the same amount of sodium chloride, yet the first tolerated approximately nine times as much water as the last before death occurred, the solution which the last received being ten times as concentrated. Intermediately placed in the

in many cases less than 1,000 cc. To be sure, he used some solutions which were hypertonic (2 per cent and 5 per cent solutions of sodium chloride and 10 per cent solutions of dextrose). The fact that Milbert's patients suffered no ill effects attributable to the rate of infusion corroborates the belief that such quantities and rates are conservative rather than radical.

It is not a new or recent observation that experimental animals tolerate the intravenous infusion of huge quantities of saline solution. Dastre and Loye<sup>3</sup> published in 1888 a convincing communication describing the introduction of suitable fluids (0.7 per cent solutions of sodium chloride) into the circulation of rabbits and dogs. They injected amounts totaling as much as three quarters of the body weight within the relatively short period of three to seven hours. These injections produced no unfavorable effects, either immediate or remote, in two months of observation. We can corroborate this result unreservedly for postinfusion periods of several days to two weeks, though we have seen no occasion to prolong the observation of recovery beyond such limits.

A. EFFECT OF MASSIVE INFUSIONS ON BLOOD PRESSURE.—The capacity of the vascular system is constantly shifting by virtue both of (1) its vasomotor reactions, which tend to adapt its capacity to the cubic measure of its contents, and of (2) the permeability of its immense capillary system, which seems to change both locally and generally in accordance with a number of different physical and chemical factors. It is therefore impossible by any means at present available to determine how long any artificially injected soluble substance remains in the circulation. This is particularly true of solutions of sodium chloride because of their extreme diffusibility.

The best that can be done is to attack the problem indirectly. A long series of tracings of blood pressure, taken during the large, rapidly administered infusions which we have employed, serves to show conclusively that the blood pressure is neither constantly nor greatly affected. A representative tracing, somewhat condensed, is reproduced in figure 1.

In general, if the blood pressure is somewhat low at the time the infusion is started a temporary rise is produced, which tends to be well sustained. If, on the contrary, the blood pressure is moderately high at the beginning of the infusion, it customarily decreases slightly within a short time and thereafter remains at about the same level throughout the infusion. In general, the blood pressure is maintained at a satisfactory level throughout a fatally large infusion and falls abruptly just

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3. Dastre, A., and Loye, P.: *Le lavage du sang*. *Arch. de physiol. norm. et path.* 2:93-114, 1888.

For the animals which died from the effects of massive doses of 1 per cent saline solution typical postmortem observations were as follows:

*General Appearance.*—The animal's abdomen was considerably distended; watery yellow fecal material was streaming from the rectum; urine was trickling from the urethra, and watery mucoid material was dripping from mouth and nose.

*Peritoneal Cavity.*—The peritoneal cavity contained some slightly blood-stained free watery fluid, the amount of which was estimated at 100 cc. (The staining with blood was probably the result of the action of dial on the peritoneum.)

*Gastrointestinal Tract.*—The walls of the stomach were thick, white and edematous; the cavity of the organ contained a small amount of bile-stained watery material. Both large and small intestine were thick, white and edematous; both were moderately filled with watery fecal material. The amount of material which the gastrointestinal tract contained was much less than one would suppose from the appearance of its various parts before incision. Most of the apparent distention which was seen from the peritoneal surface was actually due to the great thickness of the walls of the intestine.

*Pancreas.*—The pancreas was completely water logged, pale pink and friable; the structural elements of the organ were widely separated by gelatinous material. Altogether, the organ was several times its normal size. The cut surface did not exude much fluid unless squeezed or minced with a knife.

*Kidney.*—The organ showed no particular enlargement. The capsule stripped easily. Thus exposed, the organ was pale and tense and bled freely from its cut surface.

*Adrenal Glands.*—Except for some possible enlargement, the adrenal glands were apparently normal.

*Urinary Bladder.*—The bladder appeared distended, but when it was opened the appearance seemed to be due not so much to the quantity of urine it contained as to the thick, edematous condition of its walls. Such urine as it did contain was clear and colorless.

*Gallbladder.*—The gallbladder was dark bluish green and was distended with bile.

*Liver.*—Aside from some questionable enlargement, the liver presented a normal appearance.

*Retroperitoneal Space and Space Between the Leaves of the Mesentery.*—These spaces presented a remarkable appearance, as if widely distended with fluid. Cutting into the tissues, however, revealed that the appearance was due to a gelatinous edema rather than to an accumulation of free watery material. Little fluid escaped spontaneously from the cut surface.

*Thoracic Cavity.*—There was judged to be a slight excess of free fluid in the thoracic cavity. It was clear and watery in appearance, and its amount was estimated at 10 cc.

*Lungs.*—The dependent portions of both lungs were dark red and mottled; the upper lobes were pink and crepitant. The entire organ showed a frothy edema when cut and squeezed, and the lower lobes exuded a clear, serous fluid from the cut surface, which dripped when this part of the organ was compressed. Squeezing the entire organ caused frothy exudate to appear at the opening in the neck formed by tracheotomy.

*Salivary Glands.*—The salivary glands were swollen, pale and edematous.

At the risk of anticipating confirmatory physical and chemical evidence, it is suggested that after the massive infusion of essentially isotonic saline solutions death is due to no single factor. In such cases the cause of death is therefore not to be found in changes in any particular organ or system. Death probably results, rather, from a generalized physiochemical imbalance, the exact nature of which it is at present impossible to determine. It seems likely that normally reversible changes of a diffuse nature are gradually pushed further and further when the rate of infusion greatly exceeds the rate of excretion. Ultimately the organism is more or less suddenly overwhelmed, and death comes as a widespread physiochemical collapse.

This was the opinion of Dastre and Loye,<sup>3</sup> who concluded that tolerance to large intravenous infusions depended primarily on the rate of injection. If it did not exceed the combined capacities of the emunctories and the mechanisms for storage, part of the injected fluid was excreted, and the rest remained in the tissues. In such a case, they declared, accommodation was complete, and the net result was nothing more than a washing of the blood, a *lavage du sang*. When, on the contrary, the rate of injection was excessive, the emunctories could no longer increase their rate of elimination to such an extent as to keep pace with it. When this occurred, accumulation in the tissues soon exceeded the capacity for physiologic storage, and ultimately mechanical effects due to the inflow of the fluid overwhelmed the animal.

Before the discussion proceeds to other matters, the subject of accidental or adventitious death should receive some special consideration. Unless certain precautions are observed and sometimes in spite of the observance of these precautions, animals may succumb as the result of much smaller intravenous infusions of entirely compatible fluids. This is likely to occur particularly when solutions are hypertonic and when rates of injection are rapid.

The most frequent cause of these accidental or adventitious deaths is vomiting or regurgitation under conditions in which the swallowing reflex is abolished or obtunded. Under such conditions the regurgitated material may never appear at the mouth to give a hint of what is actually happening, and the usual convulsive muscular movements of the vomiting act may be in abeyance. Death occurs, nevertheless, because of aspiration of the regurgitated material into the respiratory tract, and the animal drowns in its own secretion. Doubtless the activity of the bronchial, pulmonary and salivary secretory mechanisms under the stimulation of intravenous infusion acts as a predisposing cause of this suffocation. Perhaps also the acidity of the gastric secretion which is inspired as a result of regurgitation is important as a precipitating cause. At all events, autopsy of an animal which has died for no apparent cause

work are not likely to have noted the phenomenon, for rabbits have a poorly developed vomiting mechanism. Experimenters who perform preliminary tracheotomy do not see death from this cause for the obvious reason that tracheotomized animals cannot inspire what they regurgitate. Furthermore, if the vomiting mechanism is not productive of actual regurgitation death does not ensue, and the only result is transitory hyperpnea and depression of the blood pressure, which would correspond to nonfatal "speed shock" (fig. 2).

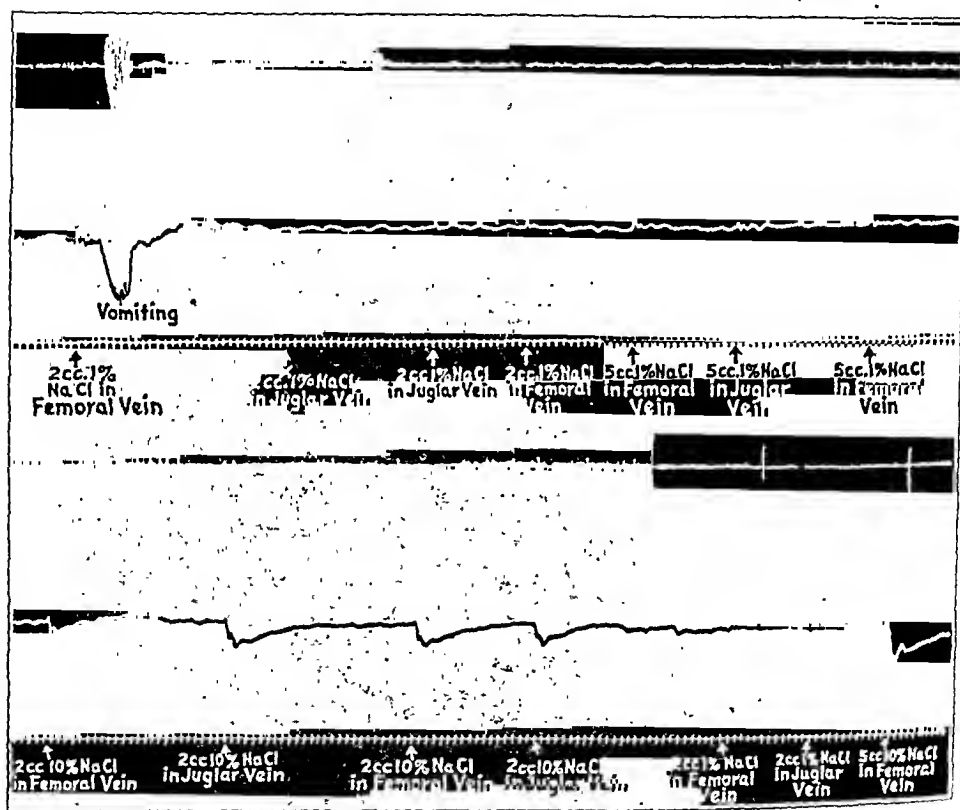


Fig. 2.—A series of attempts to produce "speed shock" by forcefully introducing small amounts of saline solution into the circulation. The very first injection (2 cc. of 1 per cent solution of sodium chloride) was followed by vomiting—extreme upper left corner. This was accidental, as indicated by the fact that repetitions of the same dose, injections of larger amounts of the same solution, and injection of small amounts of various hypertonic solutions failed to elicit the phenomenon a second time. Very hypertonic solutions (see lower panel) do produce variable momentary reductions in the blood pressure.

It is important also to avoid "pyrogenic" products in the distilled water employed in the compounding of solutions for injections and contamination of the paraphernalia used in such injections by "pyrogenic substances." The role of these substances in the production of post-

observed by a number of investigators, Priestley,<sup>7</sup> MacCallum and Benson,<sup>8</sup> Miller and Williams<sup>9</sup> and Amberg and Austin.<sup>10</sup>

Rowntree<sup>11</sup> first duplicated the symptoms of water intoxication—asthenia, muscular irritability, convulsions, salivation and ultimately death—in a series of animals by administering large quantities of distilled water by mouth. He was able to relieve the symptoms both by administering saline solution and by trephining the skull. From this he concluded that the cause of death was edema, especially edema of the brain.

Helwig, Schutz and Curry<sup>12</sup> recently reported a clinical case in which they believed the death of a 50 year old woman was caused by absorption of some 9,000 cc. of tap water from the bowel within the first thirty hours after an operation for gallstones. In a series of 7 healthy young rabbits these authors were able to produce water intoxication and death by the repeated administration of 50 cc. of tap water by rectal catheter at intervals of thirty minutes. The first indication of water intoxication was the appearance of salivation after about 500 cc. of water had been given. This was followed by fine fibrillary twitchings of the ear and muscles of the extremities after the administration of about 600 cc. After about 700 cc. had been administered clonic convulsions and marked opisthotonos developed; these signs were associated with dilatation of the pupils and decreased urinary output. Death ultimately occurred in a generalized convulsion. These authors believe that the cause of death in water intoxication is cerebral edema, though Smyth, Deamer and Phatak<sup>13</sup> in 1933 explained water intoxication on the basis of alkalosis and loss of chlorides.

Of course it is a matter of everyday observation that increasing the intake of water increases the output of urine, and it is also a truism to remark that ultimately elimination must balance intake. The point

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7. Priestley, J. G.: The Regulation of Excretion of Water by the Kidneys, *J. Physiol.* **1**:304-311, 1916.

8. MacCallum, J. B., and Benson, C. C.: On the Composition of Dilute Renal Excretions, *J. Biol. Chem.* **6**:87-104, 1909.

9. Miller, J. L., and Williams, J. L.: The Effect on Blood Pressure and Non-protein Nitrogen in the Blood of Excessive Fluid Intake, *Am. J. M. Sc.* **161**:327-334, 1921.

10. Amberg, S., and Austin, R. S., cited by Rowntree.<sup>11</sup>

11. Rowntree, L. G.: (a) Water Intoxication, *Arch. Int. Med.* **32**:157-174 (Aug.) 1923; (b) The Effect on Mammals of the Administration of Excessive Quantities of Water, *J. Pharmacol. & Exper. Therap.* **29**:135-159, 1926.

12. Helwig, F. C.; Schutz, C. B., and Curry, D. E.: Water Intoxication: Report of a Fatal Human Case, with Clinical, Pathologic and Experimental Studies, *J. A. M. A.* **104**:1569-1575 (May 4) 1935.

13. Smyth, F. S.; Deamer, W. C., and Phatak, N. M.: Studies in So-Called Water Intoxication, *J. Clin. Investigation* **12**:55-65; 1933.

In the absence of any accurate method for examining these several mechanisms individually, conclusions as to their interrelationships and relative importance must be somewhat conjectural. Large or even huge intravenous injections fail to produce sustained elevation of the blood pressure. Moreover, the ordinary methods of computing the total blood volume fail to show an increase for moderate additions of inorganic solutions to the blood stream. Accordingly, investigators in general believe that the escape of most artificially introduced solutions from the actual blood stream is rapid.

Thus Dastre and Loye<sup>3</sup> as early as 1888 computed experimentally that 75 per cent of fluids intravenously injected in large quantities passed after a short time into the tissue spaces and serous cavities of dogs and rabbits. They adduced evidence that the tissues can store with impunity amounts of such fluids equal to from one tenth to one quarter of the total body weight.

MacCallum<sup>14</sup> in 1904 obtained up to 15 per cent of fluids intravenously injected in large volumes into experimental animals from a cannula tied into the lumen of the intestine. He thus apparently demonstrated the importance of the intestine as a water emunctory under unusual conditions.

Bogert, Underhill and Mendel<sup>15</sup> in 1916 concluded as a result of experiment that the blood volume returned to normal within thirty minutes after the injection of a quantity of saline solution equal to its computed total and within so short a time as five minutes when smaller volumes were injected.

Smith and Mendel<sup>16</sup> in 1920 injected into rabbits an amount of fluid equal to the computed normal volume of blood and observed that the bulk of the injected fluid had left the blood stream within the first five minutes. They expressed the belief that the loss of this amount of fluid could not be explained on the basis of passage of water into the muscles or cellular tissues. It must, therefore, they stated, have been extravasated into the serous cavities, the stomach and the intestine, so far as it was not excreted in the urine.

Until much more is known about the normal movements of water and chlorides in the body, and especially about the forces concerned in the movement of water between the vascular tree and the extra-

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14. MacCallum, J. B.: On the Action of Saline Purgatives in Rabbits and the Counteraction of Their Effect by Calcium, *Am. J. Physiol.* **10**:101-110, 1904.

15. Bogert, L. J.; Underhill, F. P., and Mendel, L. B.: The Regulation of the Blood Volume After Injections of Saline Solutions: Studies of the Permeability of Cellular Membranes, *Am. J. Physiol.* **41**:189-218, 1916.

16. Smith, A. H., and Mendel, L. B.: The Adjustment of Blood Volume After Injection of Isotonic Solutions of Varied Composition, *Am. J. Physiol.* **53**:323-344, 1920.

determined the normal water content. In table 3 is summarized the relationship of the weights.

In table 4 are summarized the changes in water content of a number of tissues and organs after the infusion of a 1 per cent solution of sodium chloride in just sublethal amount. The figures presented in the first

TABLE 2.—*Water Content and Mass Relative to Body Weight of Various Tissues in Man and the Cat*

Organ	Percentage of Water in Organ by Weight		Weight of Organ in Percentage of Total Body Weight	
	Man	Cat	Man	Cat
Skin.....	72.03	68.3	18.0	13.94
Muscle.....	75.67	74.5	41.7	45.36
Skeleton.....	22.04	32.8	15.9	12.67
Brain.....	74.84	78.0	2.01	1.01
Liver.....	68.25	67.9	2.26	2.96
Heart.....	79.21	78.46	0.47	0.37
Lungs.....	78.96	76.3	0.69	0.51
Kidney.....	82.68	75.3	0.37	0.81
Spleen.....	75.77	78.2	0.18	0.23
Blood.....	83.00	86.7	4.90	4.46
Intestine.....	74.54	78.3	1.81	3.80

TABLE 3.—*Weight of the Separate Portions of the Gastrointestinal Tract Relative to the Total Body Weight in Cats*

Cat Number	Body Weight	Percentage of Body Weight		
		Stomach	Small Intestine	Large Intestine
1.....	2,610	1.30	3.32	0.55
3.....	2,590	1.05	3.87	0.55
4.....	2,680	1.41	4.30	0.92
5.....	2,900	0.97	2.90	0.71
6.....	3,010	1.16	4.50	0.61
7.....	3,180	0.99	2.86	0.64
8.....	2,880	1.45	3.70	0.94
9.....	2,480	0.82	2.56	0.55
10.....	2,480	1.49	4.24	0.75
11.....	2,540	1.05	3.45	0.67
12.....	2,760	0.76	2.65	0.63
13.....	1,860	0.83	3.44	0.73
Mean percentage of body weight.....		1.11	3.55	0.69
Mean percentage of body weight represented by the whole gastrointestinal tract.....			5.35	

\* This table shows great variation in the weight of all three parts of the gastrointestinal tract, stomach, small intestine and large intestine, expressed as percentage of the total body weight. In individual cases the values vary from as much as 30 per cent below to as much as 30 per cent above the mean for the entire group.

column are our own and are therefore not identical with the values quoted in table 2, though it will be noted that the agreement is very close.

As previously stated, the figures given in table 4 represent the distribution of water after virtually maximal intravenous infusions. It is a question whether this distribution of water is characteristic after infusions of various magnitudes or only after extremely large infusions. We have no direct evidence, but comparison of our results with those of Skelton, who estimated the distribution of water among some of these



Perhaps the gastrointestinal tract is an exception to this rule. Skelton<sup>17</sup> observed that it increased its water content by only 1.9 per cent after the smaller infusion which he used. He did not state, however, which portion of the tract was used for actual analysis. As has been previously explained, we were guided by differences in the gross appearance of the various portions of the tract at autopsy. We accordingly determined the values for separate portions of the tract and observed that the behavior of the stomach and colon differs markedly from that of the small intestine. The stomach and colon contain or store water in large amounts, whereas the small intestine contains or stores relatively little. If Skelton's figure for the gastrointestinal tract represents the small intestine only, this fact may be cited as another instance of close correlation between our findings and his. It then offers further evidence that the various tissues show characteristic behavior in the amount of water they store or contain, regardless of the absolute amount injected.

If, on the other hand, Skelton's figures represent the average capacity for storage of the gastrointestinal tract as a whole, our figures for the stomach and the colon are very much out of line. Such an interpretation would suggest that these tissues show an increasing affinity for water as the amount of infused solution increases. If the latter hypothesis is correct, there is a strong presumption that the stomach and colon take up the added water as a step in a process of excretion into the lumen of the intestinal canal, which thus acts as a safety valve. Certainly the fact that massive infusions frequently produce copious vomiting and watery purging may be considered to lend support to such a hypothesis.

The fact that the cerebrum definitely stores no water is of particular importance in view of the opinion of some investigators that when death results from water intoxication its immediate cause is cerebral edema.

Rowntree<sup>11a</sup> noted that cerebral edema was an outstanding feature in experimental animals in which water intoxication had been produced. The convulsive seizures and ultimate death of such animals could be prevented, he found, by decompressing the brain by means of openings made with a trephine in the skull.

Helwig, Schutz, and Curry<sup>12</sup> based their opinion that the dramatic features of water intoxication were due to cerebral edema largely on microscopic changes in the tissue. These changes were confined to the lungs, liver, brain, kidneys and bowel, and the most striking alteration was an acute swelling of the brain. The cerebral changes included definite widening of the perineural and perivascular spaces; vacuolation of the intercellular stroma; vacuolation, swelling and subependymal edema of the choroid plexus; vacuolation, swelling and desquamation of the ependymal lining of the ventricles, and vacuolation of the stroma of the cerebral substance.

Careful comparison of table 6 with table 4 shows that many of the tissues have a difference in capacity for storing the two substances. If the various tissues stored the infused solution as presented to them, viz., in the form of a 1 per cent solution of sodium chloride, the order in which the tissues appear in the two lists should be the same. The actual results are expressed mathematically in table 7.

TABLE 6.—*Normal Sodium Chloride Content of Cat Tissues and Content After Massive Intravenous Infusion of 1 per Cent Solution of Sodium Chloride*

Organ	Content in Gm. of Sodium Chloride per Kg. of Wet Organ		
	Normal	After Infusion	Percentage of Increase
Kidney.....	4.21	4.00	5.2
Liver.....	3.41	3.74	9.7
Lung.....	4.31	5.31	23.2
Duodenum.....	3.26	4.48	37.0
Pancreas.....	3.00	4.38	46.0
Skin.....	3.22	5.30	65.0
Muscle, cardiac.....	1.78	2.95	66.3
Salivary glands.....	2.75	4.86	76.0
Stomach.....	3.36	5.99	78.0
Spleen.....	2.51	4.86	94.0
Colon.....	2.69	5.58	107.0
Muscle, skeletal.....	1.05	2.42	130.0

TABLE 7.—*Evaluation of the Data Contained in Table 4 and Table 6 on the Assumption that Storage in the Tissues Is in the Form of a 1 per Cent Solution*

Organ	Gm. of Sodium Chloride per Kg. of Tissue		Ratio
	Theoretical	Observed	
Cerebrum.....	2.31	2.82	
Duodenum.....	4.80	4.48	1 : 1.06
Muscle, skeletal.....	2.60	2.42	1 : 1.08
Muscle, cardiac.....	3.20	2.95	1 : 1.08
Spleen.....	5.32	4.86	1 : 1.09
Skin.....	5.90	5.30	1 : 1.10
Liver.....	4.87	3.74	1 : 1.30
Lung.....	7.28	5.31	1 : 1.38
Kidney.....	6.00	4.00	1 : 1.50
Pancreas.....	6.90	4.38	1 : 1.57
Stomach.....	10.90	5.99	1 : 1.82
Colon.....	10.85	5.58	1 : 1.85
Salivary glands.....	11.30	4.86	1 : 2.31

As will be noted, the cerebrum acts anomalously in that it alone appears to store sodium chloride but no water. Of the remaining tissues, the duodenum, skeletal and cardiac muscles, spleen and skin store the solution most nearly in the concentration in which it is presented to them, viz., as a 1 per cent solution. Incidentally, none of these tissues are among those which take up the most water. All the other tissues store relatively far more water than sodium chloride.

chloride and by far the largest part of the water of a massive infusion within about twenty-four hours. Actually, within such a period the kidneys may eliminate more sodium chloride than was injected, and they usually eliminate more than three quarters of all the water.

TABLE 8.—*Rate of Early Elimination of Infused Sodium Chloride and Water (During the Period of Infusion)*

Cat Number	Size of Infusion (Cc. per Kg. of Body Weight)	Time in Min.	Water Eliminated (Expressed as Percentage of Amount Infused)	Sodium Chloride Eliminated (Expressed as Percentage of Amount Infused)
2B	492	85	27.0*	....
4B	550	172	32.06	....
5B	550	156	16.0	28.0
6B	725	157	31.8*	....
7B	411	74	25.0	32.0
8B	561	130	35.0*	....
9B†	427	58	9.0	10.0
10B†	439	42	7.0	9.0
16B	545	120	2.0	4.4
17B	690	150	15.7	20.5
18B	500	120	20.0	25.0
19B‡	500	122	10.0	14.0
20B	500	124	20.0	25.3
21B	408	122	14.0	16.7

\* In these animals the values were calculated on the basis of difference in weight before and after infusion; the urine was not collected.

† Animals 9B and 10B both passed copious watery stools, but the values are based solely on the urine collected.

‡ Animal 19B evacuated 130 cc. of fluid by bowel; the figures express only the elimination by kidney.

TABLE 9.—*Rate of Elimination of Infused Sodium Chloride and Water During the First Twenty-Four Hours*

Cat Number	Size of Infusion (Cc. per Kg. of Body Weight)	Time in Hours	Water Eliminated (Expressed as Percentage of Amount Infused)	Sodium Chloride Eliminated (Expressed as Percentage of Amount Infused)
5B	550	5	32	54
		20	63	95
		24.5	78	115
7B	411	5	70	95
		24	77	103
9B	427	6	47	60
		18	73	90
10B	439	5	38	48
		17	62	72
18B	500	7	47	55
		24	75	60
21B	408	7	48	59
		24	90	100

We have made a series of careful analyses of the rates of elimination of sodium chloride and water by the kidneys, which are summarized in tables 8 and 9. In table 8 appears an account of the rate of elimination of these two substances during the course of the actual infusion.

The diuretic effect of a massive infusion is shown by the kidneys within a short time after the infusion has been started, and during the actual period of administration considerable elimination occurs. During

GENERAL ACCOUNT OF THE DISTRIBUTION AND ELIMINATION OF  
MASSIVE INFUSIONS OF SODIUM CHLORIDE AND WATER

If it now is attempted, on the basis of the figures already derived, to account for the entire bulk of solutions known to have been infused into the animals, the results are at first rather surprising.

The more bulky tissues of the body, muscles, skin, intestine, liver and skeleton, together account for about 80 per cent of the total weight of the cat, as can readily be computed from table 2. It may reasonably be assumed that the skeleton, which accounts for only about 13 per

TABLE 10.—*Storage of Water and Sodium Chloride in Muscles, Skin and Gastro-intestinal Tract After Massive Infusions \**

Cat No.	Muscle		Skin		Gastrointes- tinal Tract		Liver		Total	
	Sodium Chloride	Water	Sodium Chloride	Water	Sodium Chloride	Water	Sodium Chloride	Water	Sodium Chloride	Water
2B	....	13.8	....	4.7	....	...	....	....	....	....
4B	14.4	10.8	11.3	14.0	2.56	7.6	....	....	....	....
6B	8.4	7.1	4.0	4.4	1.22	8.7	....	....	....	....
8B	7.3	11.3	7.9	11.0	1.44	6.9	....	....	....	....
16B	15.2	10.0	....	11.7	1.24	9.7	....	....	....	....
17B	7.6	7.2	5.3	4.4	1.46	5.5	....	....	....	....
Mean	10.57	10.03	7.12	8.36	1.53	7.7	1.14†	0.15†	20.41	20.24

\* All values are expressed in percentage of the total amount infused.

† Derived from previous tables.

TABLE 11.—*The Abdominal Cavity as a Reservoir for Excess Sodium Chloride and Water*

Cat Number	Quantity Infused, Cc. per Kg.	Quantity of Abdominal Fluid at End of Infusion	Sodium Chloride Content, %	Percentage of Total Infused	
				Sodium Chloride	Water
1B	590	160 cc.	....	....	9.0
2B	492	132 cc.	....	....	13.4
3B	692	110 cc.	1.000	12.20	12.2
4B	550	130 cc.	0.950	7.50	7.8
6B	725	160 cc.	0.710	9.60	13.7
8B	561	140 cc.	0.835	7.90	9.5
17B	690	115 cc.	0.780	9.96	12.7

cent of the total body weight, is incapable of storing infused solutions because of its mechanical inexpandibility. On this assumption it appears that 80 per cent of the tissues of the body account for only about 20 per cent of the infused sodium chloride and only about 26 per cent of the infused water. The derivation of these values is shown in detail in table 10.

The only other tissue which might contribute any particular addition would be the blood, but it normally accounts for little more of the total body weight than the liver. Unfortunately, the ultimate volume after infusion being unknown, its contribution cannot be computed. However, actually the value would be negligible, for the simple reason that the figures already derived include the blood content of so great a percentage of the total mass of the body.

## CONCLUSIONS

1. The lethal value for infusions of 1 per cent solution of sodium chloride in cats is of the order of 500 cc. per kilogram of body weight when the rate of injection is 5 cc. per kilogram of body weight per minute. This would correspond in a man weighing 154 pounds (70 Kg.) to 35 liters at a rate of 350 cc. per minute. Hypertonic solutions are lethal in smaller bulk and at slower rates of infusion.

2. During such massive infusions the blood pressure is neither greatly nor constantly affected. Vasodilatation and, particularly, diffusion of the solution into the tissue spaces serve to stabilize the blood pressure at an essentially normal level. At the time of death the blood pressure abruptly declines.

3. The important changes observed at autopsy are (*a*) evidences of watery vomiting and purging, (*b*) swelling of the entire animal, especially the abdomen, (*c*) the presence of a considerable amount of free fluid in the abdominal cavity, (*d*) edematous thickening of the stomach, the colon, and the urinary bladder, (*e*) gelatinous edema of the pancreas, the space between the leaves of the mesentery and the retroperitoneal space and (*f*) edema of the lungs and the salivary glands.

4. Unless pushed to a rather sharp end point of decompensation at which the blood pressure rapidly declines, infusions are not incompatible with rapid and complete recovery. The sharp end point is believed to represent some physiochemical imbalance rather than failure of any particular organ or system. Accidental death will occur in perhaps half the cases before any considerable amount of solution has been infused if precautions are not taken to prevent regurgitation, aspiration of the regurgitated material and ultimate drowning of the animal in its own vomitus. Pyrogenic substances contaminating the water used in compounding infusions may account for some premature deaths.

5. The relative weights of the various organs and tissues of the body and the water content of these tissues and organs are closely comparable as between man and the animals commonly used in the laboratory, specifically the cat. Experiments on the translocation of water following the administration of large intravenous infusions in the lower animals should therefore presumably be comparable with what occurs in man under similar conditions.

6. During and after a massive infusion both the water and the salt tend to leave the blood stream rapidly; they accumulate presumably in the tissue spaces. Relatively little water can be accommodated in such closely knit organs as the muscles and the skin, though because of their bulk their actual capacity for storage is considerable. Presumably the salt contained in the water thus stored is in essentially isotonic concentration. Organs such as the alimentary tract (except the duodenum).

## FAT EMBOLISM

### RÉSUMÉ OF THE LITERATURE PLUS SOME NEWER THOUGHTS ON DIAGNOSIS

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Unless a subject is brought before the medical profession from time to time, it may easily slip into the background and be little thought of. Since over five hundred references to fat embolism are found in the literature, only the most striking facts concerning it will be presented in this paper. Clinically, fat embolism is difficult to substantiate conclusively. This difficulty is really not the fault of medical practitioners but is due to the nature of the disease, which makes its definite recognition difficult. Some of the newer experimental phases of its diagnosis are presented in this paper in the hope that they may be of aid to the ultimate solution of the problem.

#### GENERAL SURVEY

*Historical Observations.*—As early as 1669 Lower<sup>1</sup> had injected milk intravenously in dogs, and this was probably the beginning of the knowledge of fat embolism. Magendie,<sup>2</sup> during the years 1821 to 1836, did some experimental work on hyperlipemia and its effects on the circulation in animals. His description of the experimental introduction of liquid oil into the venous circulation is classic. Zenker,<sup>3</sup> in 1862, observed the first fat emboli in the pulmonary capillaries of man after a severe crushing injury to a railroad worker. The pulmonary capillaries were seen to contain a great many emboli of fluid fat. He thought that they occurred by aspiration from the stomach through the gaping hepatic veins.

Scriba,<sup>4</sup> in 1880, reviewed all the cases up to date and then added 34 of his own. He also conducted experiments on animals and brought forth many clinical and pathologic points which had previously been

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1. Lower, cited by Flournoy, T.: *Contribution à l'étude de l'embolie graisseuse*, Paris, J. B. Baillière & fils, 1878.

2. Magendie, F.: *Leçons sur les phénomènes physiques de la vie*, Paris, J. B. Baillière, 1827, vol. 1; 1836, vol. 2.

3. Zenker, F. A., cited by Warthin, A. S.: *Internat. Clin.* 4:171. 1913.

4. Scriba, J.: *Deutsche Ztschr. f. Chir.* 12:118, 1880.

study with cottonseed oil they ascertained that if man is able to tolerate as much oil in the blood stream as a dog 120 cc. would be required for a lethal outcome. This conclusion is based on two assumptions: first, that cottonseed oil does not materially differ from the fat of the bone marrow; second, that man as well as the dog can tolerate free fat in the blood. If this is true, all the fat in the bone marrow of a femur could be well tolerated. There has been a great deal of controversy as to whether the fat is carried by the blood or by the lymph vessels. The present opinion seems to be that most of it is carried by the veins while a smaller part may be carried by the lymphatics.

It is interesting to note that experimental animals can be made to build up a resistance to experimentally induced fat embolism by repeated small injections of fat. This work was done primarily by Paul and Windholz<sup>9</sup> and later by Domanig.<sup>10</sup> They noted that such animals could withstand many times the lethal dose. No droplets of fat could be found free in the blood serum of these animals. Evidently such droplets are rapidly destroyed by a newly formed unknown substance.

*Pathogenesis and Pathologic Picture.*—After an injury to the fat of the bone marrow or adipose tissue, fat is liberated by the disintegration of the supporting fibrous tissue. Naturally there are ruptured blood vessels in the vicinity of the injury. The arteries squirt more blood into the area, thereby increasing the pressure, while the veins remain open and absorb the fatty mixture by venous suction (Miloslavich<sup>11</sup>), particularly if its consistency is more or less fluid. Gauss<sup>12</sup> brought out the point that fatty embolism is more common with fracture than with any other condition because the veins are encased in a bony wall. Hence they cannot collapse as elsewhere in the body but remain wide open for the admittance of the fatty mixture. This process may take place immediately or proceed for some time until coagulation occurs. This pathologic condition involves all the organs of the body and is too well known by all to be discussed in this brief résumé.

Lehman and McNattin<sup>13</sup> noted that fatty embolism is present in the lungs of about 50 per cent of unselected cadavers. These men have conclusively shown that anatomically the diagnosis of fatty embolism

9. Paul, F., and Windholz, F.: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **38**:614. 1925.

10. Domanig, E.: *Deutsche Ztschr. f. Chir.* **236**:693, 1932.

11. Miloslavich, E. L.: *Wisconsin M. J.* **29**:139, 1930.

12. Gauss, H.: *Pathology of Fat Embolism*, *Arch. Surg.* **9**:593 (Nov.) 1924.

13. Lehman, E. P., and McNattin, R. F.: *Fat Embolism: II. Incidence at Postmortem*, *Arch. Surg.* **17**:179 (Aug.) 1928.

appear and is of a productive nature, rarely bringing up blood-stained sputum, however. For this reason, in many of the cases the diagnosis is bronchopneumonia.

As the pulmonary arterial pressure increases, the heart must beat faster in order to overcome the circulatory resistance. The pulse rate becomes faster and stronger, and the blood pressure begins to rise. If the resistance in the pulmonic circulation increases or remains great, the heart before long begins to weaken. Its rate increases while its force decreases. The blood pressure correspondingly begins to fall. If some of the emboli lodge in the coronary vessels, the cardiac failure comes on much more quickly. Before long, the pulse becomes imperceptible, the arterial pressure falls, the venous pressure rises and the picture of deep shock and cardiac failure appears. The temperature varies from subnormal to 106 or 107 F., according to whether or not the heat-regulating center is disturbed by the emboli. The usual temperature during the height of the disease is about 103 F. In the terminal stage the temperature often rises much higher.

Petechial hemorrhages (Ryerson,<sup>6</sup> 1916) may appear in the skin, as in any other disease in which the embolic phenomena predominate. However, because the capillaries are not actually occluded, as in bacterial endocarditis, but the circulation is greatly slowed by the increased viscosity of the blood (Gauss<sup>18</sup>), they are rare. LeCount and Gauss<sup>19</sup> reported on 14 cases of death following fatty embolism in which autopsies had been done. A study of the clinical symptoms in these cases is instructive, as it gives us some idea of what occurs in cases of milder involvement which does not have a fatal outcome.

All of the patients in these cases passed from consciousness to a restless stage. In 12 this took the form of delirium, 11 becoming so violent as to require restraint. Eleven passed from delirium to the comatose state. In all 14 dyspnea was present with an associated increase in respiratory rate, the average being 53 respirations per minute. Cheyne-Stokes respiration developed in 2 cases, air hunger in 4 and a marked cough in 2. The pulse became weak and shallow and showed an average rate of 153 per minute. Involuntary passage of urine and feces occurred in 12 cases, and in the other 2 the records were incomplete. At the time of the patient's admission to the hospital the temperature was either normal or subnormal; it then rose considerably (to an average of 105.2 F. for the 14 cases). The time that the patients lived varied from two to seventeen days, with an average of six days.

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18. Gauss, H.: Studies in Cerebral Fat Embolism, *Arch. Int. Med.* 18:76 (July) 1916.

19. LeCount, E. R., and Gauss, H.: *Tr. Chicago Path. Soc.* 9:251, 1915.



in place for an hour after the operation. Simonds<sup>25</sup> observed that etherized dogs are more susceptible to fatty embolism than are those anesthetized by substances which do not dissolve fat. This is a point of some importance, and if an anesthetic which is not a solvent of fat can be used as efficiently and safely it should be given preference.

Warthin<sup>21</sup> advised the following prophylactic management:

1. Avoidance of unnecessary or rough handling of patients.
2. Immediate splinting and early reduction of all fractures (Tanton<sup>26</sup>).
3. Use of a saw in preference to the chisel in orthopedic operations, if possible (Lexer<sup>27</sup>).
4. Slow removal of Esmarch's bandage (Buerger<sup>28</sup> and Aberle<sup>29</sup>). Reiner<sup>30</sup> advised canaliculizing the vein, allowing the first blood after removal of the constrictor to flow out. Czerny<sup>31</sup> and fifty years later Wegelin<sup>32</sup> advocated intravenous injection of sodium carbonate, probably with the idea of forming a soluble soap. This method has fortunately received but little support. All experimental animals died under this regime. The active treatment of this condition is very poor, and many of the suggested methods are not only theoretically but practically in error.

Czerny<sup>31</sup> advised venesection to lessen the venous congestion. Schanz<sup>33</sup> stated the belief that physiologic solution of sodium chloride administered both intravenously and by hypodermoclysis is of benefit. Bissell,<sup>34</sup> however, expressed the opinion that such a procedure is contraindicated because of increased pressure on the right side of the heart. Wilms<sup>35</sup> suggested drainage of the thoracic duct. Fritsche<sup>36</sup> observed experimentally that this procedure is beneficial if done at the first appearance of the symptoms. Gröndahl<sup>22</sup> noted that even ligation of the femoral vein and removal of the inguinal glands did not prevent fatty embolism. Wilms<sup>35</sup> advised incising the area of fracture and

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25. Simonds, J. P.: A Study of Low Blood Pressures Associated with Peptone Shock and Experimental Fat Embolism, *J. A. M. A.* **69**:883 (Sept. 15) 1917.

26. Tanton, J.: *J. de chir.* **12**:287, 1914.

27. Lexer, E.: *Lehrbuch der allgemeinen Chirurgie*, ed. 3, Stuttgart, Ferdinand Enke, 1908.

28. Buerger, L.: *Vrtljschr. f. gerichtl. Med. (supp.)* **39**:159, 1910.

29. Aberle, R.: *Ztschr. f. orthop. Chir.* **19**:89, 1907.

30. Reiner, M.: *München. med. Wchnschr.* **54**:2004, 1907.

31. Czerny, V.: *Berl. klin. Wchnschr.* **12**:593, 1875.

32. Wegelin, C.: *Schweiz. med. Wchnschr.* **4**:133, 1923.

33. Schanz, A.: *Zentralbl. f. Chir.* **37**:43, 1910.

34. Bissell, W. W.: Amount of Fat in the Blood Stream of Persons with Broken Bones, *J. A. M. A.* **67**:1926 (Dec. 23) 1916.

35. Wilms, M.: *Semaine méd.* **30**:138, 1910.

36. Fritsche, E.: *Deutsche Ztschr. f. Chir.* **107**:456, 1910.

These observations, therefore, have conclusively proved to me that it is not the total fat content of the blood in which one should be interested, but the state in which this fat occurs. If it is in the form of a stable emulsion, no fat droplets are present in the blood, and therefore no embolism can occur. On the other hand the corpuscular fat content is of all importance, as it causes the occlusion of the vessels which produces the embolic phenomena. Unfortunately, only 5 per cent of the total fat content of the blood is found in this form. If one considers that the total fat content, as has been stated before, is only 0.4 per cent, one realizes that corpuscular percentage almost approximates zero. Therefore, it stands to reason that any total chemical method for determining increases or decreases of this substance would be far beyond the scope of quantitative chemical determinations, as the percentage of error introduced by the best present day methods would be too great.

Other fields of experimental work were sought for possible aid in determining the fat content of the blood. The use of the spectroscope was suggested. However, both a physicist and an excellent physiologist stated that the concentration of fat was too small to produce any appreciable variations. At a later date the possibility of measuring electric conductivity in order to determine changes in the fat content of the blood serum was discussed. This method as well as the use of the polariscope received negative comment and was abandoned.

#### RESULTS OF DARK FIELD EXAMINATIONS OF THE BLOOD IN CASES OF RECENT FRACTURE AND IN CONTROL CASES

Edmunds<sup>43</sup> first described the dark field examination of the blood for particles of fat in 1877. Further work along these lines was carried on by Neumann<sup>44</sup> in 1907. Gage and Fish<sup>45</sup> in 1924 published a most excellent article on this subject, describing investigative work on absorption and assimilation of fat in the lower animals. The senior author was the first to give the microscopic particles of fat in the blood the name of chylomicrons (1920), meaning that they are 1 micron in diameter and are composed of chyle.

A control study of 25 miscellaneous blood serums from the medical wards of the Cook County Hospital was undertaken. No variations from the normal were found. Several creamlike specimens of blood from a lactating woman yielded a few interesting observations. In spite of a cholesterol content of 335 mg. per hundred cubic centimeters and

43. Edmunds, J.: *Monthly Micr. J.* **18**:78, 1877.

44. Neumann, A.: *Zentralbl. f. Physiol.* **21**:102, 1907.

45. Gage, S. H., and Fish, P. A.: *Am. J. Anat.* **34**:1, 1924.

urine and blood in the Cook County Hospital failed to reveal a single instance of droplets of free fat in the centrifuged specimen of either the urine or the blood. Eleven of the specimens of blood showed chylous emulsion, but it was physiologic, for the blood had been drawn within an hour or two after the ingestion of a fatty meal. We next studied fluids obtained in 50 cases of fracture from one to one hundred and forty-four hours after the accident. In not a single instance were we able to find any free fat droplets in specimens of either the urine or the blood.

From the work just described it may be safe to assume that the presence of droplets of fat (larger than a chylomicron) in specimens of either the urine or the blood is indicative of free intravascular fat, which is consistent with fat embolism. However, the examination of these liquids requires long centrifuging, staining of the supernatant liquid with sudan III and careful study of the fluid. Many trials are necessary before one learns the technic.

#### THE VALUE OF ROENTGENOGRAMS OF THE CHEST IN THE DIAGNOSIS

In an attempt to bring further aid to the diagnosis of this condition, Jirka and I<sup>48</sup> proved by experimental work on dogs that roentgenograms of the chest show definite changes in the lungs after intravenous injection of oil. This work will be carried on in human beings when the opportunity presents itself. As far as I know, the roentgen ray has never been used as an aid to the diagnosis of fat embolism. For this reason I am presenting for the first time an evaluation of the use of roentgenograms of the chest for this purpose. Eleven dogs were used in the experiments, animals weighing close to 12.5 Kg. being selected whenever possible. Sterile oleic acid was given intravenously to 6 and sterile olive oil to 5 of the animals. Varying doses were used. One must not lose sight of the fact that fat embolism is not a true embolism in the sense of a permanent occlusion of a vessel. It is simply a retardation of the flow of blood through a capillary while the droplets of oil become elongated and are slowly forced from the arterial to the venous side of the circulation.

#### CONCLUSIONS

1. It has been demonstrated conclusively that a diagnosis of the embolism can be made during life by the use of modern diagnostic methods.

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48. Jirka, F. J., and Scuderi, C. S.: Fat Embolism: An Experimental Study on the Value of Roentgenograms of the Chest in Diagnosis, *Arch. Surg.* 33:708-713 (Oct.) 1936.

# NORMAL ANATOMY AND VARIATIONS OF THE PERIPHERAL NERVES OF THE LEG AND FOOT

APPLICATION IN OPERATIONS FOR VASCULAR DISEASES:  
STUDY OF ONE HUNDRED SPECIMENS

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The treatment of obliterative vascular disease by peripheral nerve block was first reported by Silbert<sup>1</sup> (1922), the posterior tibial nerve having been blocked with alcohol for relief of pain in thromboangiitis obliterans. Carlette<sup>2</sup> (1929) reported his method of cutting the terminal sensory branches subcutaneously above a painful ulcer of the malleolus. Smithwick and White<sup>3</sup> (1930) reported 11 cases in which alcohol was injected and Allen<sup>4</sup> (1932) 29 cases from the same clinic in which similar treatment was employed. In 1933 Laskey and Silbert<sup>5</sup> reported on 18 patients treated by the division and immediate suture of the peripheral nerves. The procedure was recommended to avoid sloughs due to spilling or seepage of alcohol and because occasionally the entire sensory nerves were not blocked by means of alcohol. Smithwick and White<sup>6</sup> (1935) reported a total of 45 cases; in the later ones the block was effected by crushing the nerves rather than by injecting alcohol. The nerves were crushed for a distance of  $\frac{1}{4}$  inch (0.6 cm.) if regeneration within three months was desired and of  $\frac{1}{2}$  inch (1.3 cm.) if anesthesia was to be prolonged for six months.

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From the Daniel Baugh Institute of Anatomy, Jefferson Medical College.

1. Silbert, S.: A New Method for the Treatment of Thrombo-Angiitis Obliterans, *J. A. M. A.* **79**:1765 (Nov. 18) 1922.

2. Carlette, C. E.: A Rapidly Curative Operation for Irritable Ulcer of the Malleolus, *Surg., Gynec. & Obst.* **48**:811, 1929.

3. Smithwick, R. H., and White, J. C.: Elimination of Pain in Obliterative Vascular Disease of the Lower Extremity, *Surg., Gynec. & Obst.* **51**:394, 1930.

4. Allen, A. W.: Results Obtained in the Treatment of Raynaud's Disease by Sympathetic Neurectomy and in Thrombo-Angiitis Obliterans by Desensitization of Peripheral Sensory Nerves, *Ann. Surg.* **96**:867, 1932.

5. Laskey, N. F., and Silbert, S.: Thrombo-Angiitis Obliterans, *Ann. Surg.* **98**:55, 1933.

6. Smithwick, R. H., and White, J. C.: Peripheral Nerve Block in Obliterative Vascular Disease of the Lower Extremity, *Surg., Gynec. & Obst.* **60**:1106, 1935.

secting manuals, English, French and German, reveals not infrequently an incongruity and inadequacy of detail in discussion of the sensory nerves of the lower extremity.

In the belief that the maximum benefit by this method is obtained only by location of the nerve with the least possible trauma, I undertook the study of (a) the most conservative approach for each sensory nerve of the foot and (b) the most constant anatomic location of each nerve at a site above the terminal (sensory) divisions and below all important motor divisions. For this investigation 70 lower extremities were carefully studied, many of which were dissected with the cooperation of members of the freshman class. The proper surgical approach and the principles suggested by these studies were applied on 30 additional specimens, so that a total of 100 lower extremities were investigated.

#### SAPHENOUS NERVE

*Average Diameter, Course and Relations.*—The average diameter of the saphenous nerve is  $\frac{3}{8}$  inch (0.3 cm.). It is the real terminal branch of the femoral nerve. It accompanies the femoral artery to the hiatus in the adductor muscle, passes along the tendon of the adductor magnus to the medial side of the knee joint and pierces the fascia lata near the tendon of the sartorius muscle. It passes downward subcutaneously behind the medial border of the tibia just posterior to the great saphenous vein, giving off the medial crural cutaneous branches to the skin of the medial and anterior surfaces of the leg. It divides into two branches, of which the smaller continues along the margin of the tibia to the ankle while the other passes in front of the internal malleolus. The latter is then distributed to the skin on the medial side of the foot and extends as far as the medial side of the great toe, anastomosing with the medial branch of the superficial peroneal nerve.

*Branches and Their Variations.*—In 89 of the specimens examined the nerve divided into its two terminal branches 6 inches (15 cm.) above the internal malleolus. The larger branch left the medial border accompanied by the internal saphenous vein, to cross anteriorly 4 or 5 inches (10 to 12.5 cm.) above the internal malleolus. Of the remaining 11 cases, the terminal branching occurred 5 inches (12.5 cm.) above the internal malleolus in 5, 3 inches (7.5 cm.) above in 3 and 2 inches (5 cm.) above in 3.

*Sensory Distribution and Most Constant Site.*—The nerve therefore supplies the surface of the medial and anterior aspects of the calf and leg and the medial surface of the instep and of the ball of the big toe (fig. 1). The most constant site was noted to be 7 inches (18 cm.) above the internal malleolus at the medial border of the tibia, posterior

digitorum longus muscles, the lower part of the tibia and the posterior ligaments of the ankle joint; posterior are the gastrocnemius and soleus muscles above and the deep fascia below. Anterior to the ligamentum laciniatum, between the internal malleolus and the medial prominence

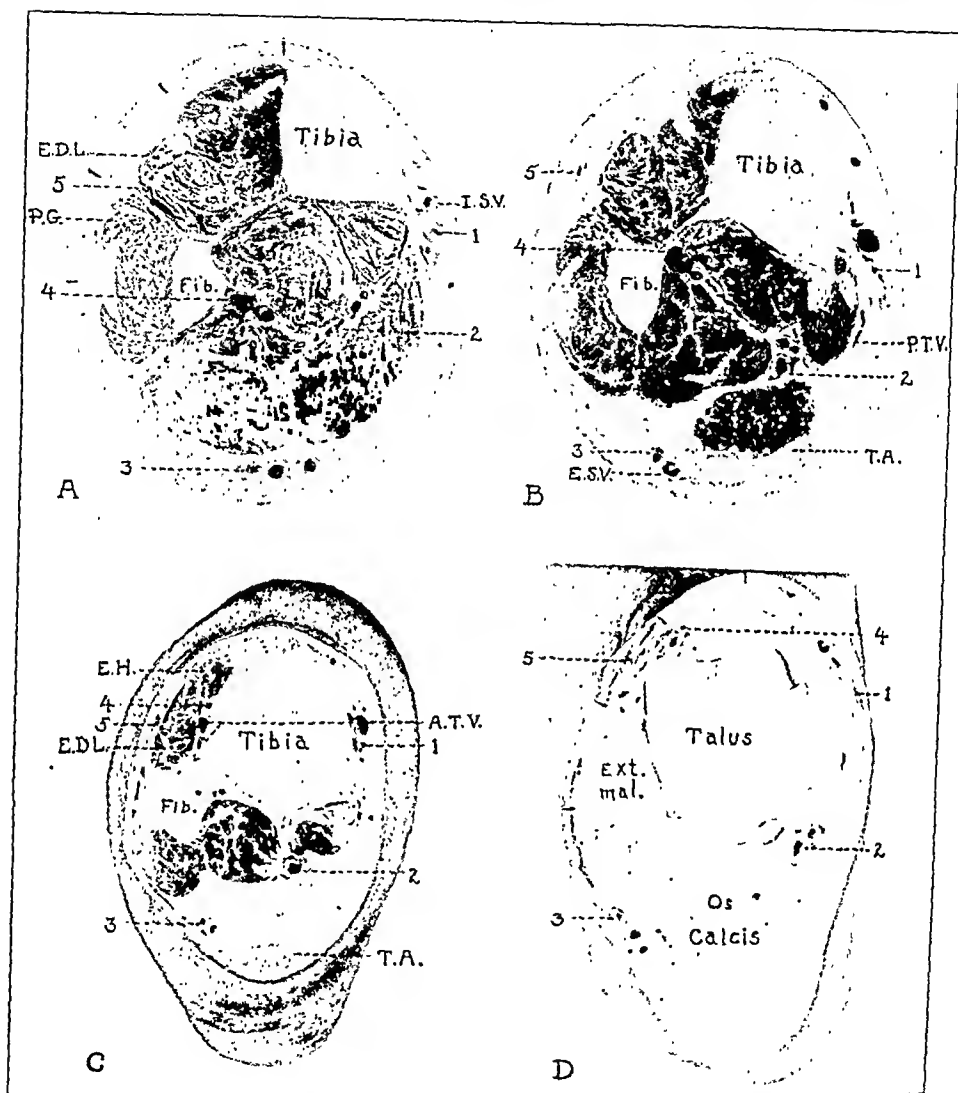


Fig. 2.—Cross sections made (A) 6 inches (15 cm.) above the internal malleolus, (B) 3½ inches (8.9 cm.) above the internal malleolus, (C) 1½ inches (3.8 cm.) above the internal malleolus and (D) at the level of the tip of the internal malleolus. The nerves are indicated as follows: 1, saphenous; 2, posterior tibial; 3, sural; 4, anterior tibial, and 5, superficial peroneal. *I.S.V.* indicates the internal saphenous vein, *E.S.V.* the external saphenous vein, *P.T.V.* the posterior tibial vessels, *A.T.V.* the anterior tibial vessels, *E.D.L.* the extensor digitorum longus, *P.G.* the peroneal muscle group, *T.A.* the achilles tendon and *E.H.* the extensor hallucis longus. Note the superficial peroneal nerve in A, the saphenous nerve in A, the posterior tibial nerve in B, the sural nerve in B and the anterior tibial nerve in C and D.

of the calcaneus, the nerve divides into its plantar divisions  $\frac{1}{2}$  to 1 inch (1.3 to 2.5 cm.) proximal to the division of the artery.

*Branches and Their Variations.*—Muscular branches arise in the popliteal space and extend to the triceps surae, popliteus and plantaris muscles and to the tibialis posticus, flexor digitorum longus and flexor hallucis longus muscles below the fossa.

The terminal plantar nerves are formed  $\frac{1}{2}$  inch (1.3 cm.) above and behind the tip of the internal malleolus. The smaller posterior division immediately gives off the medial calcaneal branch or branches. In 4 cases this branch arose from the posterior tibial nerve directly, in 3 coming off 1 inch (2.5 cm.), and in the fourth 3 inches (7.5 cm.), above the site of terminal division. In 4 instances the posterior tibial nerve was split for a distance of 2 inches (5 cm.), 3 to 4 inches (7.5 to 10 cm.) above the internal malleolus, by a small twig off the posterior tibial artery.

The medial plantar nerve divides into muscular and cutaneous twigs and digital branches to the skin of the plantar surface of the medial aspect of the big toe and adjacent surfaces of the second, third and fourth toes. The lateral plantar division supplies the remaining part of the fourth and fifth toes by its superficial branch; the deep division gives off muscular and articular twigs.

*Sensory Distribution and Most Constant Site.*—The nerve therefore supplies the cutaneous surface of the medial part of the heel and the plantar surface of the foot and toes (fig. 1). The most constant site is 3 inches (7.5 cm.) above the tip of the internal malleolus, directly in the line of the medial border of the achilles tendon and at a depth of  $\frac{3}{4}$  inch (1.9 cm.), anterior to the deep fascial covering of the flexor digitorum longus (figs. 2 B and 3 B).

*Surgical Approach.*—A 1 to  $1\frac{1}{2}$  inch (2.5 to 3.8 cm.) incision, its center 3 inches (7.5 cm.) above the tip of the medial malleolus, is made in line with the medial border of the achilles tendon. At a depth of  $\frac{3}{4}$  inch (1.9 cm.) the fascia posterior to the flexor digitorum longus is incised and the nerve is exposed lateral to the posterior tibial artery and its venae comites, the largest component of this neurovascular bundle (fig. 3 B).

#### SURAL NERVE

*Average Diameter, Course and Relations.*—The average diameter of the sural nerve is  $\frac{1}{8}$  inch (0.3 cm.). Its medial cutaneous branch arises from the tibial nerve in the popliteal space, runs down the calf in the groove posterior and between the two heads of the gastrocnemius muscle with the small saphenous vein. At the middle of the leg it pierces the crural (deep) fascia, joining with the peroneal anastomotic branch of the lateral sural cutaneous nerve shortly thereafter to form

and the extensor digitorum longus laterally. At the ankle it divides into a medial and a lateral branch.

In 95 cases the nerve lay lateral to the artery and its venae comites in the upper and middle parts of the leg, then passed anterior to the artery 4 inches (10 cm.) above the ankle joint and in the lower 2 inches (5 cm.) of the leg again lay lateral or anterolateral to the vessel. In 4 cases the nerve was lateral, then passed posterior to the artery and then medial to it, while in 1 case it lay lateral, then anterior and then medial to the anterior tibial artery.

Sabotta and McMurrich illustrated the nerve as coursing at first lateral, then posterior and then medial to the artery and its venae comites. Testut, Morris (ninth edition) and Gray (twenty-first edition) illustrated the nerve as first lateral, then anterior and then medial to the artery. As already noted, the former relation occurred in 4 cases and the latter in only 1 case, and these should not be represented as anatomic normalities but rather as infrequent variations.

*Branches and Their Variations.*—The nerve divides into two terminal branches. In all the cases in this series except 2 this division occurred  $\frac{1}{2}$  inch (1.3 cm.) above the ankle joint. In one of the exceptional cases it occurred  $2\frac{1}{2}$  inches (6.4 cm.) above, and in the other at the level of, the astragalotibial joint. The medial branch lies lateral to the dorsalis pedis and at the base of the first interosseous space pierces the deep fascia to supply articular twigs, muscular twigs to the first interosseous muscle and cutaneous branches to the contiguous surfaces of the great and second toes. The lateral branch supplies articular branches and muscular twigs to the extensor digitorum brevis muscle.

*Sensory Distribution and Most Constant Site.*—The nerve supplies only the dorsal contiguous surfaces of the first and second toes (fig. 1). The most constant site is 1 inch (2.5 cm.) above the astragalotibial joint anteriorly beneath the cruciate crural ligament, and between the extensor hallucis longus muscle medially and the extensor digitorum longus laterally. It lies lateral or anterolateral to the anterior tibial artery and its venae comites.

A less constant site is  $2\frac{1}{2}$  inches (6.4 cm.) above this joint, between the extensor hallucis longus muscle laterally and the tibialis anticus medially. Here the nerve lay anterior to the artery and its venae comites in 96 of the cases and posterior in 4 (figs. 2 C and D and fig. 3 D and E).

*Surgical Approach.*—A 1 inch (2.5 cm.) incision is made, its center 1 inch (2.5 cm.) above the ankle joint anteriorly at the juncture of the outer two thirds and medial third of the surface of the skin of the anterolateral quadrant of the leg (fig. 2 D). The cruciate crural



mediate division supplies the intermediate portion of the dorsum of the foot, dividing into two branches. One supplies the adjacent surfaces of the third and fourth toes; the other terminates in the fourth and fifth toes and anastomoses with the sural nerve.

*Sensory Distribution and Most Constant Site.*—The nerve therefore supplies the anterior surface of the lower one third of the leg and the region of the ankle, the medial and intermediate parts of the dorsum of the foot and the dorsum of all the toes except the adjacent surfaces between the first and second toes (fig. 1). The most constant site is 5 inches (10.5 cm.) above the tip of the external malleolus, just within the anterior border of the fibula, in the groove between the peroneal group of muscles and the extensor digitorum longus. The nerve was found exiting through the crural (deep) fascia and lying in the subcutaneous tissues in 91 of the cases. In 9 cases the nerve was found beneath the deep fascia (figs. 2 *A* and 3 *F*).

*Surgical Approach.*—A 1 inch (2.5 cm.) incision is made, its center 5 inches (12.5 cm.) above the tip of the external malleolus and in the palpable groove between the peroneal group of muscles and the extensor digitorum longus. This site is at the juncture of the lateral third and the medial two thirds of the surface of the skin of the anterolateral quadrant of the leg (fig. 2 *A*). The nerve was found subcutaneously in 91 of the cases. If the nerve is not located, the deep fascia is to be incised, for it lay deeply in 9 cases (fig. 3 *F*).

to be rapidly progressive, the reactive phases of the tubercle—encapsulation, fibrosis, calcification and ossification—are not observed, the lesion showing only central caseation. On the other hand, when the process of healing occurs it is accompanied by some or all of these characteristic changes. These evidences of bodily reaction do not necessarily mean complete quiescence of the lesion. Local or general spread of the disease may take place within the cranial space, as elsewhere, even after more or less complete healing has taken place.

The behavior of tuberculous infection in the intracranial and intraspinal spaces varies considerably in different cases. In most instances the lesion occurs in the form of leptomeningitis. Whether in such cases the miliary tubercles represent the primary lodgment of bacilli as a result of blood stream infection (as in generalized miliary tuberculosis) or, as some have argued, a secondary spread from some pre-existing tubercle is of no vital moment in this connection.<sup>1</sup>

In a smaller number of cases autopsy discloses one or more discrete tubercles lodged in the substance of the brain, with or without miliary tubercles in the leptomeninges. The tubercles may be small, in which case they are often multiple and at times numerous. Occasionally, however, a large solitary mass is found which is capable of provoking an increase in intracranial pressure. Patients with such a lesion not infrequently come to operation with a diagnosis of intracranial tumor, and the surgeon may be entirely unaware of the nature of the lesion until the microscope makes it clear.

Certain pathologic characteristics of tuberculomas of the brain should be emphasized. It is of interest that while they may be found in any or all parts of the brain they tend to develop in the cerebral or cerebellar cortex, probably because of the more abundant blood supply of this structure. The tendency of solitary tubercles to be situated in the cerebellum is as yet unexplained.<sup>2</sup> True caseation, with its characteristic softening, is never found in tuberculomas of the brain; instead there is

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1. It has seemed to us that the theory that tuberculous meningitis is due to a secondary spread of infection from a preexisting tubercle lacks something to make it entirely convincing. The presence of a tubercle is not a priori evidence that the new infection has come from this source. On the other hand, the presence of cerebral tubercles of different sizes in certain instances suggests that "showers" of organisms have reached the brain on several different occasions. Further, observations in such cases do not indicate that the infection has spread concentrically about the primary tubercle, as usually happens when leptomeningitis is consequent to surgical interference with a gross tuberculoma. On the contrary, the miliary nodules are clustered primarily about the branches of the middle cerebral arteries, which strongly suggests that the organisms arrived by these channels. The subject needs further study before it can be considered closed.

2. Ehlers, H., and Courville, C. B.: Solitary Tuberculoma of the Cerebellum, *Bull. Los Angeles Neurol. Soc.* 1:81, 1936.

and 43 cases of tuberculoma of the brain. In 3 cases the tuberculomas were either calcified or calcified and ossified. The incidence of "healed" tubercles in our series would therefore be 1 in 5,000 miscellaneous cases (0.02 per cent), 1 in 135 cases of tuberculous meningitis (0.7 per cent) and 1 in about 15 cases of tuberculoma of the brain (6.6 per cent).

#### REVIEW OF THE LITERATURE

In a study of intracranial tumor published in 1864, Ogle<sup>9</sup> reported 2 calcified tuberculomas in 75 cases of calcified tuberculous lesion collected over a period of twenty-two years. Lancereaux and Lackerbauer<sup>10</sup> reported a case of calcified tuberculoma in the left optic thalamus; the lesion had apparently been present for over sixty years. In Foà's case<sup>11</sup> a calcified tuberculoma, apparently quiescent, was found in the left cerebellar hemisphere of a 12 year old boy who died of nephritis. The first case in which a diagnosis of calcified tuberculoma was made roentgenographically was that of Klieneberger.<sup>12</sup> The diagnosis was never verified. In a discussion of the roentgen aspects of the problem, Ström<sup>13</sup> described a case in which the diagnosis was verified surgically and cited the cases of Siemon<sup>14</sup> and Sabat.<sup>15</sup> Another case in which the lesion was discovered by roentgen examination (post mortem) was that described by Stewart.<sup>5</sup> Other cases in which the diagnosis was verified by operation or by roentgen examination were described by Marie, de Martel and Behague,<sup>16</sup> Cushing,<sup>17</sup> Paterson and Stevenson<sup>18</sup> and Vincent,

9. Ogle, J. W.: Cases Illustrating the Formation of Morbid Growths, Deposits, Tumors, Cysts, etc., in Connection with the Brain and Spinal Cord, and Their Investing Membranes, *Brit. & For. M.-Chir. Rev.* **34**:457, 1864.

10. Lancereaux, E., and Lackerbauer, M.: *Atlas d'anatomie pathologique*, Paris, G. Masson & fils, 1871, p. 395.

11. Foà, P.: Tubercolo cerebellare guarito, *Gior. d. r. Accad. di med. di Torino* **9**:403, 1903.

12. Klieneberger, Carl: Die Radiographie intracranieller Prozesse in der inneren Medizin, mit besonderer Berücksichtigung der radiographisch darstellbaren Hirntumoren, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **14**:106, 1909.

13. Ström, S.: Ueber die Röntgendiagnostik intrakranieller Verkalkungen, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **27**:577, 1919-1920.

14. Siemon, G. S.: Ausgedehnter Defect und teilweise verknöcherter Tumor der linken Grosshirnhemisphäre, Atrophie der rechten Kleinhirnhemisphäre und der linken Olive, *Inaug. Dissert.*, Marburg, 1893; cited by Ström.<sup>13</sup>

15. Sabat: Aus der Röntgendiagnostik der Erkrankungen des Kopfes und der Wirbelsäule, *Verhandl. d. deutsch. Rönt.-Gesellsch.* **9**:101, 1913; cited by Ström.<sup>13</sup>

16. Marie, P.; de Martel, and Behague, P.: Ablation d'un tubercule intracranien: Guérison du malade, *Rev. neurol.* **36**:1109, 1920.

17. Cushing, H.: The Intracranial Tumors of Preadolescence, *Am. J. Dis. Child.* **33**:551 (April) 1927; *Intracranial Tumours*, Springfield, Ill., Charles C. Thomas, Publisher, 1932, pp. 114-115.

18. Paterson, J. E., and Stevenson, W. D. H.: Case of Healed Tuberculoma of the Brain: Operative Removal, with Pathological Report, *Glasgow M. J.* **113**: 281, 1930.

Author	Age	Sex	Pathologic Observations	Source of Infection	Comment
Ogle, 1861 (case 1).....	36	F	Calcified tuberculoma in vultum interpositum; ventricles distended, ependymal granulations; thickened arachnoid	Shoulder and lungs	Symptoms for 1 mo.
(case 2).....	Child		Calcified tuberculoma size of hazelnut in right cerebellar lobe	Not stated	Epileptiform convulsions
Laurenceux and Lackerbauer, 1871..	65	M	Calcareous tuberculoma size of hazelnut in left optic thalamus	Lungs	Right hemiparesis since age of 4 yr.
Siemon, 1895 (quoted by Ström).....	?	?	Calcified tuberculoma 4.5 by 2.5 by 2 cm. in ventral part of frontal lobe; bony formation and calcareous crystals demonstrated histologically	Not stated	
Foix, 1903.....	10	M	Calcified tuberculoma deep in left cerebellar hemisphere; meningitis; slight hydrocephalus	Not stated	
Subat, 1909 (quoted by Ström).....	17	?	Calcified tuberculoma size of walnut in inferior portion of right frontal and parietal lobes	Not stated	Jacksonian fits and hemiplegia on left
Kilneberger, 1909-1910.....	12	M	Calcified tumor in region of corpora quadrigemina (diagnosed as tuberculoma by roentgenogram and tuberculin test)	Unknown	
Ström, 1910-1921.....	21	F	Calcified tuberculoma size of plum in left frontal lobe, verified by operation; calcareous material and bony formation shown microscopically	Unknown	Symptoms for 13 yr.
Marle, de Martel and Behague, 1920.	18	M	Tuberculoma size of mandarin orange in left frontal lobe, verified by operation; microscope demonstration of calcareous material in tubercle	Tuberculous glands in cervical region	Jacksonian convulsions, paralysis of right arm; alive after operation
Stewart, 1927.....	27	M	Calcified tuberculoma size of hazelnut in right cerebellar lobe; demonstrated by roentgenogram after death, verified at autopsy	Tuberculous glands of cervical region	Death from Addison's disease
Smith, 1927.....	62	M	Tuberculomas in right cerebral hemisphere and lenticular nucleus; calcareous material demonstrated microscopically	Unknown; mother died of tuberculous	"Stroke" at 4½ yr.; dragged left foot, tremor right hand
Cushing, 1927.....	14	M	Progressive calcification of tuberculoma exposed at operation; not verified histologically	Pulmonary tuberculous	Intracranial pressure; alive 7 yr. after operation
Puterson and Stevenson, 1930.....	16	M	Tuberculoma of right parietal lobe; calcareous material demonstrated microscopically	Not given	Convulsions at 2 and 5 yr.; mental symptoms at 13; still alive after operation
Vincent, Hleuyer and Vogt, 1933.....	8	M	Tuberculoma size of hazelnut in right parieto-occipital region; roentgen and histologic demonstration of calcification; tissue removed at operation	Not stated; father died of tuberculous	Symptoms for 6½ yr.; alive 32 mo. after operation
Borchardt, 1933.....	7	M	Four small conglomerate tuberculomas, exact location not stated; calcification demonstrated roentgenographically and histologically	Pulmonary tuberculous	Symptoms for 4½ yr.; died of tuberculous meningitis
Evans and Courville, 1938 Case 1.....	8	M	Large calcified tuberculoma 6 by 7.5 cm. in right parieto-occipital region; demonstrated roentgenographically before death	Pulmonary tuberculous	Symptoms of increased pressure, aphasia and left hemiplegia for 5 yr.
Case 2.....	10½	M	Calcified tuberculoma 3 by 1.3 by 0.7 cm. in right frontal lobe; noncalcified tuberculoma in left cerebellar hemisphere	Tuberculous tracheobronchial lymph nodes	"Tuberculous meningitis" at 3 yr.; general convulsions at 10 yr.
Case 3.....	6	..	Calcified and ossified tuberculomas in right frontal lobe (1 by 0.5 cm.) and left frontal and parietal lobes (2 to 6 cm.)	Probably pulmonary tuberculous	Listlessness and irritability for 3 wk. before death

\* In all the cases the diagnosis was verified at autopsy unless otherwise stated.

irregular, yellowish white calcareous mass (fig. 2). Sections were taken from this and from adjacent areas for microscopic study.

A section from the central calcareous portion of the tuberculoma disclosed an irregular shell of calcification composed of a fusion of many small crystals. The interior of the shell was structureless. This calcareous formation was surrounded by a fibrous connective tissue scar which had undergone almost complete hyalinization. In the adjacent cerebral tissue the blood vessels had become calcified, the tissue being studded with a large number of round or oval darkly stained granules. The nerve cells in the region were also "calcified,"<sup>22</sup> the encrusted cells still retaining to a great extent their original form.

Sections from the peripheral portion of the tuberculoma showed the typical characteristics of such a lesion: lymphocytes, plasma cells, fibroblasts and giant cells.

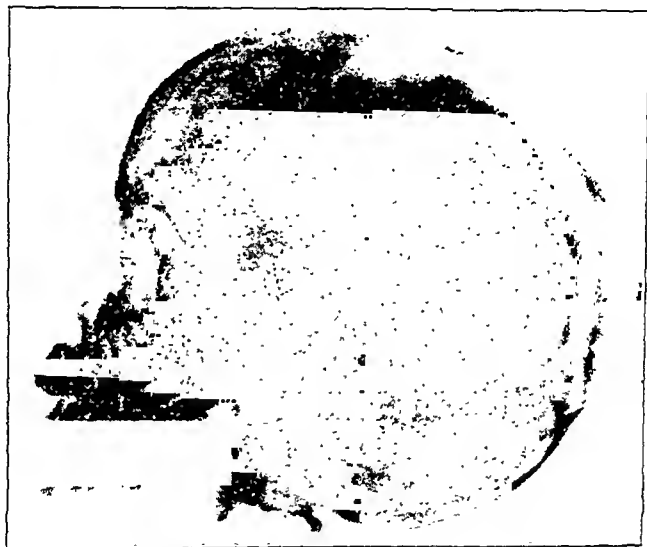


Fig. 1 (case 1).—Roentgenogram of the skull, showing the calcareous mass in the right parietal region. The thinned cranial vault with increased convolutional markings, separation of the suture lines and erosion of the dorsum sellae are all indicative of long-continued increased intracranial pressure.

*Comment.*—This case presents a number of unusual features. The long, continuous course suggests the progressive growth of the tuberculoma. This is further suggested by the characteristic structure of the peripheral portion of the tuberculoma. One might predicate another possibility, however: that a recurrence of activity had occurred in the peripheral portion of the tuberculoma after its central portion had

22. The incrustation of nerve cells with salts which stain deep blue in routine preparation of sections has long been designated as "calcification." These cells are actually covered with a deposit of iron salts, which can be demonstrated by the prussian blue method. The test is imperfect when used in tissues fixed by immersion in formaldehyde for long periods, as was the case in this specimen.

A Mexican boy 3 years of age was admitted to the Los Angeles County Hospital in February 1926 with a story of suddenly becoming ill two weeks previously, after exposure to dampness. Pains in the legs and back were followed by generalized convulsions and vomiting of four days' duration. The child had lost his appetite.

On examination, a bilateral internal squint was noted, associated with retraction of the head and bilateral Brudzinski and Kernig signs. Lumbar puncture disclosed opalescent spinal fluid in which a pellicle promptly formed. The fluid was not under increased pressure. There were 525 cells per cubic millimeter, the type of which was not stated. A roentgenogram of the chest was reported as showing no evidence of tuberculosis. The boy was discharged on March 1 with a diagnosis of tuberculous meningitis.

The child was next seen in the clinic on June 17, 1930, with a deformity of the right foot (equinovarus) thought to have resulted from infantile paralysis, which he had contracted three years before. There were two draining ulcers on the dorsum of this foot.

The boy subsequently contracted osteomyelitis of the metatarsal bones of the left foot. Because of its character the lesion was suspected of having a tuberculous origin, although no acid-fast organisms were ever found in the exudate. The left leg was finally amputated in its middle third. The bony lesion proved to be of a tuberculous nature.

A roentgenogram was taken of the chest on July 25, 1931, when the child was brought to the clinic with a chronic papular eruption of the skin. No evidence of pulmonary tuberculosis could be made out.

On Jan. 1, 1932, the boy was readmitted to the hospital with a swelling of two weeks' duration in the right thoracic wall over the seventh rib in the anterior axillary line. A roentgenogram showed alterations in the rib suggestive of osteomyelitis secondary to an abscess in the soft tissues. Resection of the rib was done. Some exudate from the lesion was injected into a guinea pig; subsequently typical tubercles developed in the animal and characteristic acid-fast organisms were recovered. The child was ultimately referred to the Children's Hospital. There was persistent drainage from the recent operative wound, from the stump of the left leg and from sinuses in the region of the sacro-iliac joints.

In October 1933 otitis media on the left developed; this was complicated by mastoiditis followed by generalized convulsions with lateralizing manifestations on the right side. Mastoidectomy was done at the Children's Hospital on October 26.

On March 19, 1934, the boy was readmitted to the County Hospital with a low grade fever and advanced emaciation. There was drainage from the left mastoid wound as well as from the other sites just mentioned. The right knee was swollen and tender. The breath sounds were harsh throughout the chest and were associated with occasional crackling rales at the base of the right lung. The patient died on October 14, at the age of 10½ years, seven years after the onset of his illness.

An autopsy was performed three hours after death by Dr. Eugene Joergensen. Draining sinuses were present in the left mastoid region, in the medial aspect of the supracondylar region of the right arm, in the right anterior axillary line over the seventh and eighth ribs, in the right anterior superior iliac spine, in the lateral aspect of the right knee and in the stump of the left leg.

There were no areas of ulceration or caseation in the lungs. The tracheo-bronchial glands were enlarged and showed considerable caseation. Exploration of the various draining sinuses showed them to be extensive and complicated and associated with the formation of large abscesses.

sleep. The past history was essentially negative except for uncomplicated chicken-pox two months before admission. A left internal squint had been present since birth. There was no known contact with tuberculosis.

The child was lethargic and appeared to be chronically ill. The skin over the trunk and extremities was dry and scaly. The pupils were regular and equal and reacted sluggishly to light. An old perforation was observed in the left tympanum; the right was perforated with numerous minute openings. The cervical glands were slightly enlarged. The neck was moderately stiff. Impaired resonance over the upper anterior part of the left lung was associated with bronchial breathing. The deep reflexes showed no irregularities. Kernig and Brudzinski signs were elicited.

Lumbar puncture disclosed a clear, colorless fluid under more than 400 mm. of pressure. There were approximately 100 cells per cubic millimeter, consisting of

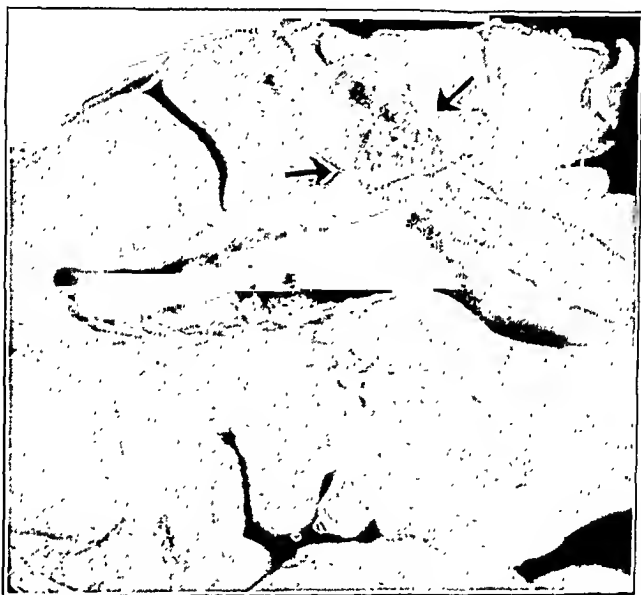


Fig. 3 (case 2).—Small calcified tuberculoma in the subcortical white matter of the right frontal lobe. The dilated lateral ventricle was the result of chronic thickening of the arachnoid with adhesions to the pia in the cisterna magna and in the cisterna pontis lateralis.

both lymphocytes and polymorphonuclears, the proportions not being stated. Repeated punctures done almost daily disclosed a clear fluid consistently under high pressure and containing between 70 and 80 cells per cubic millimeter, predominantly lymphocytes. It required from 22 to 24 drops of spinal fluid to reduce Benedict's solution. Quantitatively, the sugar varied between 30 and 40 mg. and the chlorides between 610 and 680 mg. per hundred cubic centimeters. Levison's test constantly gave negative results. Wassermann and Kahn tests were negative. There were 16,000 white cells per cubic millimeter of blood, with 92 per cent polymorphonuclears.

A roentgenogram of the chest showed increased density throughout the left hilar and perihilar regions.

Death came on July 19.

THE SIGNIFICANCE OF CALCIFICATION AND OSSIFICATION IN  
TUBERCULOMA OF THE BRAIN

Deposition of calcium salts and, less commonly, formation of true bone are consequences of healing in tubercles, regardless of their location. These processes occur typically in the lymph nodes along the respiratory passages and in tubercles of the lung. Because of the more

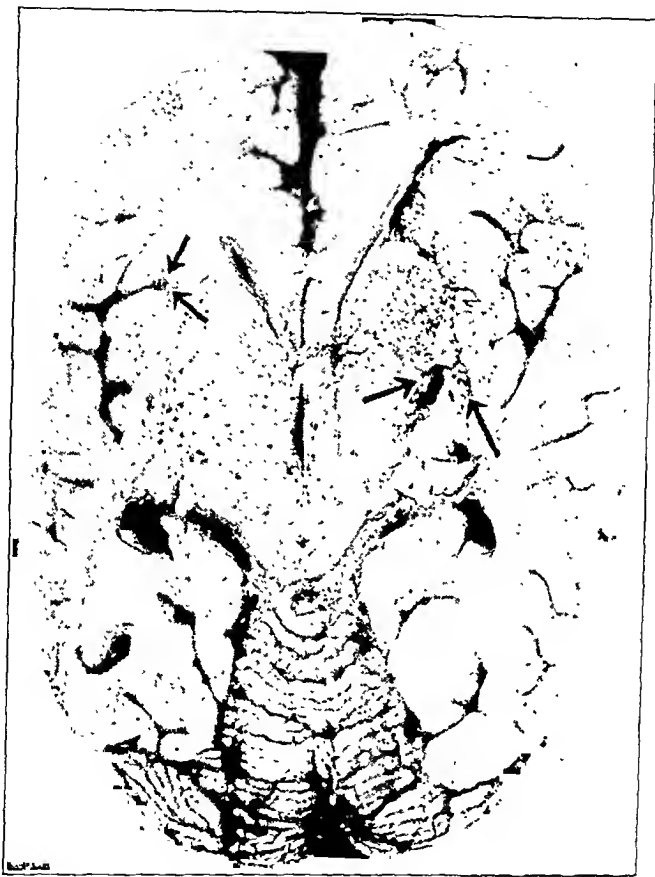


Fig. 4 (case 3).—Horizontal section of the brain, showing extensive softening of the right basal ganglia and centrum of the right frontal lobe and external capsule. A small calcified tuberculoma was observed (arrows) in this area. On the left side were seen several small calcified and ossified tubercles (arrows) in the leptomeninges.

malignant character of tuberculous inflammation in the meninges and brain, healing of tubercles in these structures is much less common, and calcification and ossification would therefore be observed less frequently. As has been repeatedly emphasized, healing of a tubercle in the brain or elsewhere is not absolute evidence of complete quiescence. "Healed"



The second type of calcification is similar to the one just described, in that calcium is deposited in blood vessels within the tuberculoma (fig. 6). The vessels are quite clearly shown in the histologic preparation, which suggests that complete necrosis has not taken place. The presence of the calcium is probably to be accounted for in a similar way.

In the third type, which is the common and characteristic one, calcification follows more marked regressive changes in the lesion. In fact, identifying remains of the tuberculoma are usually not observed, and it has often been difficult or impossible to identify the lesion. We

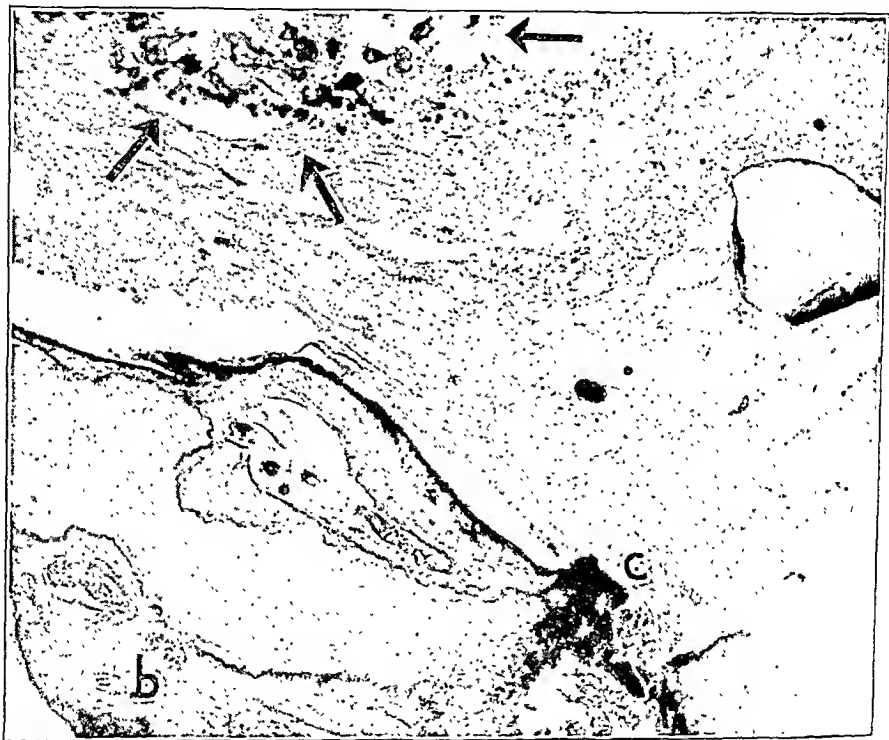


Fig. 5 (case 3).—Calcification of blood vessels (arrows) in the brain tissue at the margin of the tuberculoma, in which both calcification (*c*) and formation of bone (*b*) have occurred. Hematoxylin and eosin stain;  $\times 45$ .

shall show, however, that the process of calcification and ossification is characteristic of the lesion and that one can be assured of the original nature of the lesion on this basis. In our cases this conclusion is made certain, for in case 1 calcification occurred only in the central portion of an unusually large tuberculoma, and in cases 2 and 3 the association of calcified and typical noncalcified lesions made the situation obvious.

The lesion consists of three well defined zones or areas: (1) an outer zone of hyalinized connective tissue, (2) a more or less irregular calcareous shell and (3) a structureless necrotic core. The outer layer

the connective tissue capsule, probably explains the collapse and fracture of the calcareous shell.

It is of importance in this connection to learn whether calcification in tubercles is identical regardless of the type of tissue in which the lesion is situated. A survey of the literature on the characteristics of calcification in tuberculomas has largely been fruitless. Scattered remarks in textbooks indicate the calcification to be central,<sup>25</sup> as is the case in experimental tubercles.<sup>26</sup> Actual study of a calcified tubercle in a

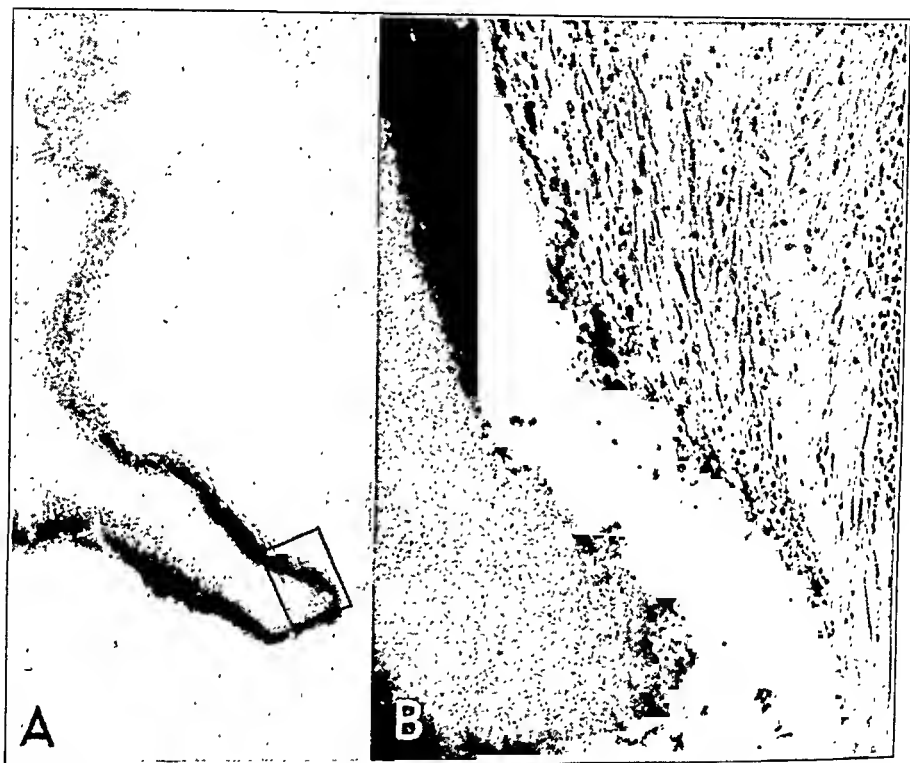


Fig. 7 (case 1).—Calcareous shell in tuberculoma of the brain. *A* shows a portion of the irregular, contracted shell with a structureless, necrotic center;  $\times 30$ . *B* shows an enlarged portion of the shell, which is composed of myriads of crystals of calcium salts;  $\times 145$ . Hematoxylin and eosin stain.

mediastinal lymph node showed a calcareous shell, although the central core was small. This suggests that the process is essentially the same,

25. Delafield, F., and Prudden, T. M.: *A Text-Book of Pathology*, ed. 15, revised by Frances Carter Wood, Baltimore, William Wood & Company, 1931, p. 717.

26. Spies, T. D.: The Calcification of Tubercles by Means of Irradiated Ergosterol, *Am. J. Path.* 6:337, 1930; The Calcification of Tubercles by Means of Irradiated Ergosterol in Experimental Chronic Tuberculosis, *Am. Rev. Tuberc.* 23:169, 1931.

From this purely morphologic study, the relative importance of these three factors—impaired tissue respiration, formation of fatty acids and hyalinization of connective tissue—in the process of calcification cannot be determined. One can only state that the process begins in a zone just within the external margin of the tuberculoma, probably at the juncture of the central necrotic area and the peripheral border of granulation tissue. Thus is formed a calcareous shell, which ultimately becomes irregular and broken as the connective tissue at the border contracts and the necrotic material in the center is slowly absorbed.

This explanation, however, does not suffice for the occasional calcification of small vessels in the central necrotic regions. In such cases necrosis with occlusion of blood vessels is apparently not complete, and the theory of disturbed tissue respiration would apply more particularly.

The formation of bone within a tuberculoma is evidently much less common, if the facts gathered from a survey of the literature and from our own experience are of any significance. For example, we found in the report of Siemon the only definite statement that bony formation was present in a tuberculoma. It occurred in a tuberculoma in but 1 of our cases, but in this case it occurred also in a number of miliary tubercles which had also undergone the process of calcification. The bone which is present is characteristic of new-formed osteoid tissue in which calcium has not yet been deposited (fig. 8). A study of the details in our case is of interest. Either the bone developed within the area in which calcium had been deposited, or calcium was laid down in the new-formed bone in the same way as it was in the hyalinized connective tissue, namely, in the form of conglomerations of calcareous crystals (fig. 9). The appearance of the lesions lends strength to the conception of Nicholson<sup>29</sup> that the presence of calcareous salts in an abnormal situation tends to stimulate the connective tissue cells in this region to undergo a metaplasia into bone cells.<sup>30</sup>

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29. Nicholson, G. W.: *The Formation of Bone in a Calcified Epithelioma of the Skin*, *J. Path. & Bact.* **21**:287, 1916-1917.

30. This brings up the interesting problem as to the actual mechanism of bone formation in abnormal situations. Our observation again seems to bear out the theory of R. Leriche and A. Policard (*The Normal and Pathological Physiology of Bone*, St. Louis, C. V. Mosby Company, 1928) that bony formation is not the secretory product of a specific cell but is rather the result of a transformation of connective tissue cells to osteoblasts and that the resulting osteoid tissue is transformed into true bone by a subsequent deposit of calcium. This is evidently an entirely different process than that occurring, for example, in a case of metastatic osteogenic sarcoma of the brain, in which formation of bone was evidence of a specific cellular tendency to perform this function (Harding, W. G., and Courville, C. B.: *Bone Formation in Metastases of Osteogenic Sarcoma: Report of Case with Metastases to the Brain*, *Am. J. Cancer* **21**:787, 1934).

Formation of bone seems to take place deep within the calcareous shell, where in turn an irregular and usually incomplete bony shell may occur. At times only small areas of the shell may become ossified (fig. 10).

From our observations one would conclude that the formation of new bone is a later process, occurring some time after calcium has been deposited. In fact, it is probably encouraged by the presence of calcareous salts, which tend to stimulate the metaplasia of connective tissue cells into osteoblasts. The reported cases are too few and the details



Fig. 10 (case 3).—Formation of bone in a conglomerate meningeal tubercle. *A* shows two separate calcareous shells with capsules, the larger of which has collapsed. Calcium has also been deposited in the regional blood vessels (arrows);  $\times 24$ . *B* shows the detail of the bony formation, which is assuming adult type with deposit of calcium. Calcareous salts in the shell (upper right) and in the capsule (right) are also shown;  $\times 96$ . Hematoxylin and eosin stain.

too obscure for one to draw any conclusions as to the length of time required for this process.

#### SUMMARY AND CONCLUSIONS

1. The occurrence of calcification or ossification in tubercles of the brain, evidently indicative of partial or complete healing of these lesions.

# CALCIFICATION ABOUT THE FLEXOR CARPI ULNARIS TENDON

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During the past year or so we have had an opportunity of studying a number of patients, all of whom presented such strikingly similar symptoms as to warrant their being grouped together as having a definite clinical entity. Typically, there were sharply localized pain and tenderness over the area around the pisiform bone; a pathognomonic limitation of motion at the wrist; occasional signs suggesting an inflammatory reaction; a characteristic roentgenogram, and early subsidence of symptoms. When we referred to the literature for some help in understanding the condition, we were afforded scant assistance. Except for a single case reported by Cohen<sup>1</sup> and the casual statement of Codman<sup>2</sup> that he knew "of one case in the flexor carpi ulnaris," no mention could be found of the condition, either in the clinical or in the roentgenologic literature. Neither Codman nor Cohen presented any histologic evidence to justify their belief that the site of the lesion was the tendon itself. We are inclined to share the opinion of Codman and Cohen, but we can offer no positive proof and the present consideration is undertaken from clinical rather than from pathologic interest.

Though all of our cases showed a basic similarity, there seemed to be sufficient variation to justify subdivision of the conditions into three main types similar to those suggested for injuries to the supraspinatus tendon: (1) a hyperacute form, (2) an acute form with calcification and (3) an acute form without calcification.

## THE HYPERACUTE FORM

### REPORT OF CASE

CASE 1.—H. H. G., a 29 year old man, was admitted to the hospital on Dec. 9, 1935, complaining that two days before he had noted a dull pain in the left wrist while making a plaster of paris splint. During the day the pain became more

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From the service of Dr. Harry Finkelstein at the Hospital for Joint Diseases.

1. Cohen, I.: *Am. J. Surg.* 38:172, 1924.

2. Codman, E. A.: *Boston M. & S. J.* 154:613, 1906; *The Shoulder*, Boston.

The Author, 1934, pp. 68-83.

bone. The swollen area was aspirated in an effort to determine the presence of pus, but none was obtained.

During the forty-eight hours following his admission to the hospital the patient was given hot hand baths, and the pain gradually subsided. At this time a roentgenogram revealed that there was a distinct diminution in the density of the previously mentioned small body below the ulnar styloid process. Irregular calcification was distributed longitudinally from a point immediately below the styloid process of the ulna, downward into the soft tissues and externally to the pisiform bone, for about 1 inch (2.5 cm.). The neighboring bones showed no specific alteration. Roentgenographically, the appearance was extremely unusual, and not



Fig. 2 (case 2).—The shadow in this case is circular, as if it were enclosed in a limiting membrane, such as a bursa.

characteristic of any pathologic process. The roentgenogram suggested calcification in the ligamentous structures of the part. On the fifth day pain had completely disappeared. A roentgenogram subsequently taken for check-up purposes revealed complete disappearance of any densities, and all irregularities in the wrist had completely disappeared. (An almost identical process subsequently developed at the insertion of the triceps.)

#### THE ACUTE FORM WITH CALCIFICATION

CASE 2.—M. P., a 50 year old woman, was first seen in the outpatient department on Nov. 9, 1936. There was a history of pain, redness and swelling over

mittent pain which occurred only on exertion, the patient received no treatment and continued at his work. Two days before his admission to the hospital the pain suddenly became excruciatingly severe, and the patient was forced to discontinue playing the cello. Examination revealed marked tenderness over the left pisiform bone, directly at the insertion of the flexor carpi ulnaris. There was moderate swelling, but no inflammation and no redness. Dorsal and radial deviation caused extreme pain. A roentgenogram (fig. 3) showed a hazy, serpentine calcification, which suggested periostitis, and a destructive process in the pisiform bone. Experience had, however, taught us to discount this roentgen picture. The

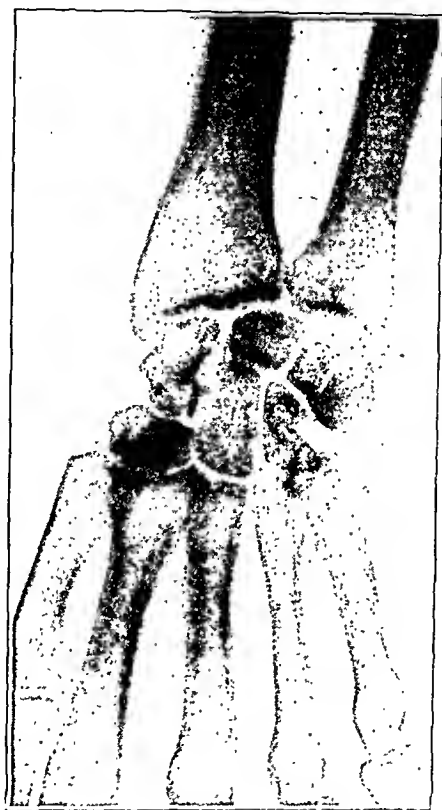


Fig. 4 (case 4).—The irregular, oval shadow is located nearer the tip of the ulna than in the other cases.

patient's hand was strapped, and he was given several applications of short wave therapy and a mild analgesic. Within three days the symptoms had completely disappeared, and the patient was able to resume his usual activities.

CASE 4.—The patient was a private patient of Dr. Harry Sonnenschein, who gave us permission to reproduce the roentgenogram. The details of the case are not available, but it is reported that several months after a fracture of the elbow the patient suddenly began to complain of severe pain in the wrist. A roentgenogram (fig. 4) showed the typical calcification. The wrist was immobilized, and within three or four days the symptoms of pain, swelling and limitation of motion had vanished completely.

with radiation of the discomfort up the forearm. The onset had been sudden, and there had been no injury. No other joints were involved.

Examination revealed redness, tenderness and swelling along the course of the lower end of the right flexor carpi ulnaris tendon. Pain was elicited on extension, and relief was obtained by flexion of the wrist.

Treatment consisted of application of a dorsal plaster splint, with the wrist in moderate flexion, and gentle radiant heat. The patient was last seen one week later, on Nov. 25, 1936, and he was completely relieved except for slight tenderness, which we later heard disappeared in a short time.

#### COMMENT

Though we have reported a relatively insignificant number of cases, we believe the condition described is more common than has been realized. It is hoped that the future will disclose many additional instances of the disability. Because the affliction has been of such short duration and has responded readily to conservative therapy, we have not felt justified in removing pathologic material. However, we are hopeful that this defect in our presentation may be remedied shortly. In the absence of any pathologic specimen we have been forced to infer the location of the calcium deposition. Anatomically considered, the site of the pathologic process may be: (1) the occasional bursa subadjacent to the flexor carpi ulnaris, (2) the peritendinous soft tissues, (3) the tendon itself. From a clinical point of view, the syndrome here presented resembles in many respects that described for the supraspinatus tendon by Codman, Brickner,<sup>3</sup> Moschcowitz<sup>4</sup> and others. It resembles also a similar condition found in the gluteus medius muscle, which has more recently been described by Goldenberg and Leventhal.<sup>5</sup> Though it is known that in both the supraspinatus and the gluteus medius tendon the biologic process probably consists of calcification and later ossification in an area of necrosis in a tendon, the former condition is still erroneously referred to as subacromial or subdeltoid bursitis, while the latter is described as peritrochanteric bursitis or as calcareous gluteal bursitis. The same possibility for misapprehending the location of the calcification presents itself with the flexor carpi ulnaris tendon as with the other two tendons just mentioned, for an occasional bursa is to be found between the tendon and the volar aspect of the pisiform bone, which forms part of its insertion. This bursa appears to have been first described by Monroe,<sup>6</sup> who stated that there is a very small bursa between the tendon of the flexor carpi ulnaris and the os pisiforme.

3. Brickner, W.: *Am. J. Surg.* **30**:108, 1916; *Am. J. M. Sc.* **149**:351, 1915.

4. Moschcowitz, E.: *Am. J. M. Sc.* **150**:115, 1915.

5. Goldenberg, R. R., and Leventhal, G. S.: *J. Bone & Joint Surg.* **18**:205, 1936.

6. Monroe, A.: *Outline of the Anatomy of the Human Body in Its Sound and Diseased State*, Edinburgh, A. Constable & Co., 1813, vol. 1, p. 471.



was, however, finally dismissed, and the patient was operated on under general anesthesia on Nov. 21, 1936, with the provisional diagnosis of tumor of the left wrist.

An incision was made over the volar aspect of the wrist, extending slightly over the thenar eminence, apparently in the region of the flexor carpi radialis tendon. This tendon was cut down on, and a very definite lime salt incrustation

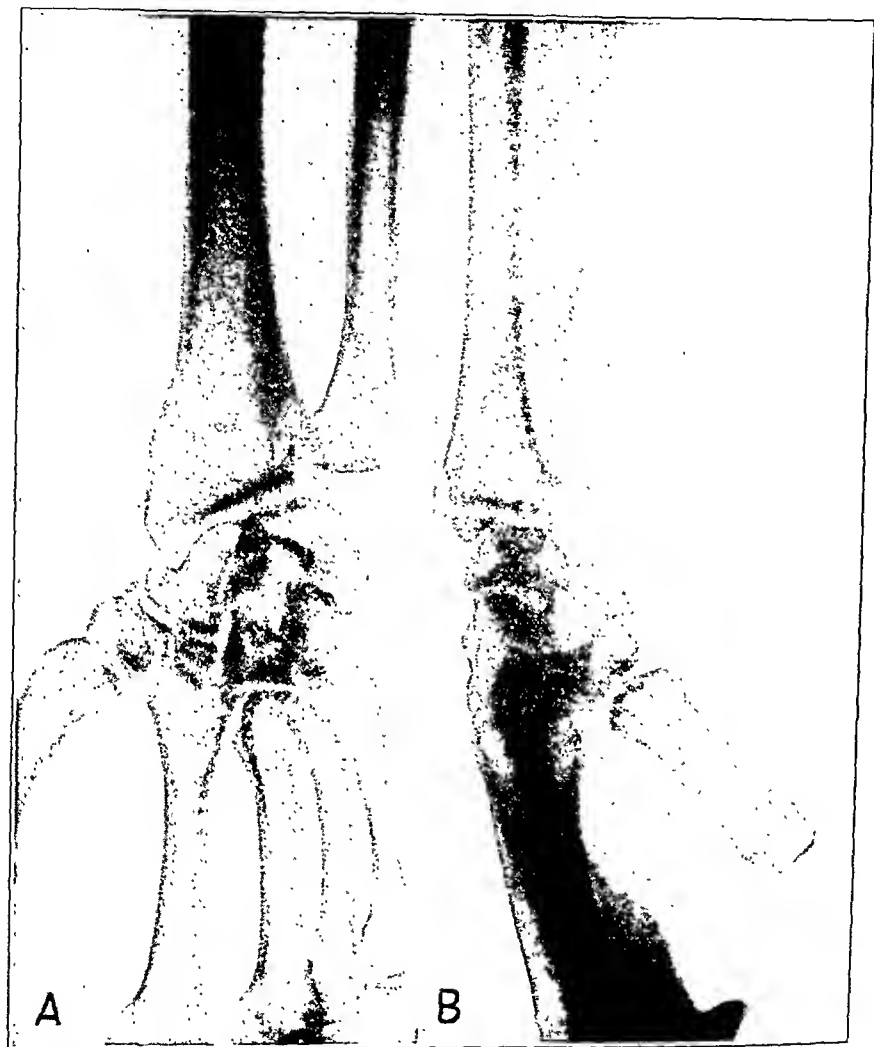


Fig. 5 (case 9).—*A*, anteroposterior view, showing a small, oval, calcific shadow between the greater multiangular and the navicular bone. *B*, lateral view, showing the volar position of the radio-opacity, which at operation was found to be a calcification in the sheath of the tendon.

was found within the substance of its sheath. The incrustation was removed in toto and the wound closed in layers. Because of the small size of the incision, there appears to have been some doubts as to the exact tendon about which the calcification was found. This is, of course, immaterial. The important point is, as Dr. Steindler assured us in another letter, under date of March 3, 1937, that

Clinically, the condition must be differentiated from a stenosing tendovaginitis or an acute infectious process, such as cellulitis or osteomyelitis. Roentgenographically, it must be differentiated from osteomyelitis or periostitis of the pisiform bone, an accessory carpal ossicle,

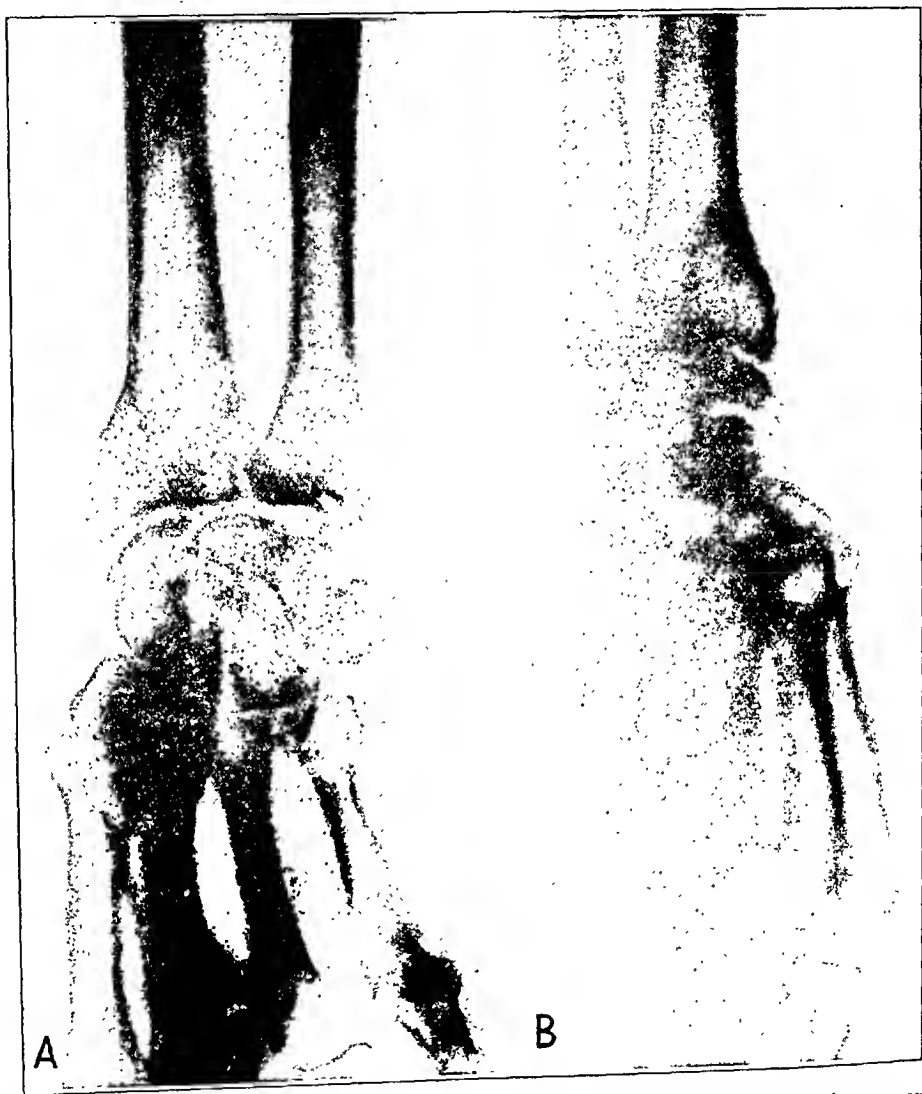


Fig. 6.—*A*, anteroposterior view, showing radio-opacities simulating those seen in the other figures. The patient had a history of a Colles fracture, with fracture of the ulnar styloid process. *B*, on lateral view the radio-opacities were found dorsally and ventrally situated, probably representing fragmentation and healing in a fractured ulnar styloid process.

or an old, comminuted fracture of the ulnar styloid. In the case of one patient whom we recently examined there was a definite history of fracture (fig. 6). Careful lateral and oblique roentgenograms dem-

# CHANGES IN THE MAMMARY GLAND OF THE RAT PRODUCED BY VARIOUS GLANDULAR PREPARATIONS

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During our recent investigation<sup>1</sup> of the influence of endocrine substances on the development of the mammary gland of the rat, a number of mammary abnormalities were experimentally induced. The possibility that some of these observations may have a bearing on diseases of the human breast made it desirable to study the changes further.

It is our purpose in this paper to present the more pertinent results and to suggest their possible relation to mammary disease in human beings.

A number of workers have observed abnormalities in the mammary glands of animals into which various endocrine substances were injected. Evans and Simpson<sup>2</sup> noted extensive mammary development following injection, for long periods, of pituitary extracts into rats; excessive epithelial proliferation and formation of fibro-adenoma occurred in non-castrated females. No effect was obtained in castrates, since the changes are mediated through an effect on the ovaries. Howard<sup>3</sup> recently obtained similar results in noncastrated adult female rats treated for several months with pituitary preparations or with extracts of the blood of pregnant women.

Marked abnormalities of the mammary gland resulting from excessive estrogenic stimulation have been reported. Goormaghtigh and

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This study was aided by a grant from the Anna Fuller Fund.

From the Surgical Pathological Laboratory, Department of Surgery, Johns Hopkins Hospital and Johns Hopkins University School of Medicine.

1. Astwood, E. B.; Geschickter, C. F., and Rausch, E. O.: Development of the Mammary Gland of the Rat: A Study of Normal, Experimental and Pathologic Changes and Their Endocrine Relationships, *Am. J. Anat.* **61**:373, 1937.

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The effect of estrogen on the incidence of mammary cancer has been variously reported. Lacassagne<sup>11</sup> in an extensive series of articles described the effect of estrogen on male mice of certain strains, the females of which are highly susceptible to spontaneous cancer of the breast. These males, after extensive development of the mammary gland similar to that of normal females, showed epithelial proliferation, dilatation of the ducts and, after six to eighteen months, malignant change. These experiments seem to show that the feminization of males with mammary development places them in the genetic category of their sisters and that both males and females inherit the predisposition to cancer. Similar results have been obtained by Cramer and Horning<sup>12</sup> and by Gardner, Smith, Allen and Strong.<sup>13</sup> This subject has been thoroughly covered recently by Suntzeff, Burns, Moskop and Loeb,<sup>14</sup> who found that treatment with estrogen modifies the incidence of mammary cancer in susceptible strains. It has not yet been established that estrogenic treatment will initiate the formation of cancer in otherwise nonsusceptible animals.

The relation of mammary diseases in human beings to abnormalities of the female reproductive organs has recently been reviewed by Taylor,<sup>15</sup> who attempted to correlate pain in the breast and formation of tumor with ovarian dysfunction. These studies should lead to further investigation of the mammary changes which so commonly occur in persons who present other evidence of endocrine dysfunction.

#### VARIATIONS IN MAMMARY STRUCTURE

An important consideration in the evaluation of abnormal changes in the breast is variation in the histologic picture and in the physiologic response in different portions of the same breast. In the human breast structural differences in various parts of the gland are difficult to interpret because of the complex distribution of the ducts and the density

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11. Lacassagne, A.: Hormonal Pathogenesis of Adenocarcinoma of the Breast, *Am. J. Cancer* **27**:217 (June) 1936.

12. Cramer, W., and Horning, E. S.: Experimental Production of Estrin of Pituitary Tumors with Hypopituitarism and of Mammary Cancer, *Lancet* **1**:247 (Feb. 1) 1936.

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Fig. 2.—Whole mount ( $\times 18$ ) of a mammary gland of a normal 75 day old female rat, showing the normal postpuberal architecture characteristic of the non-pregnant adult female.

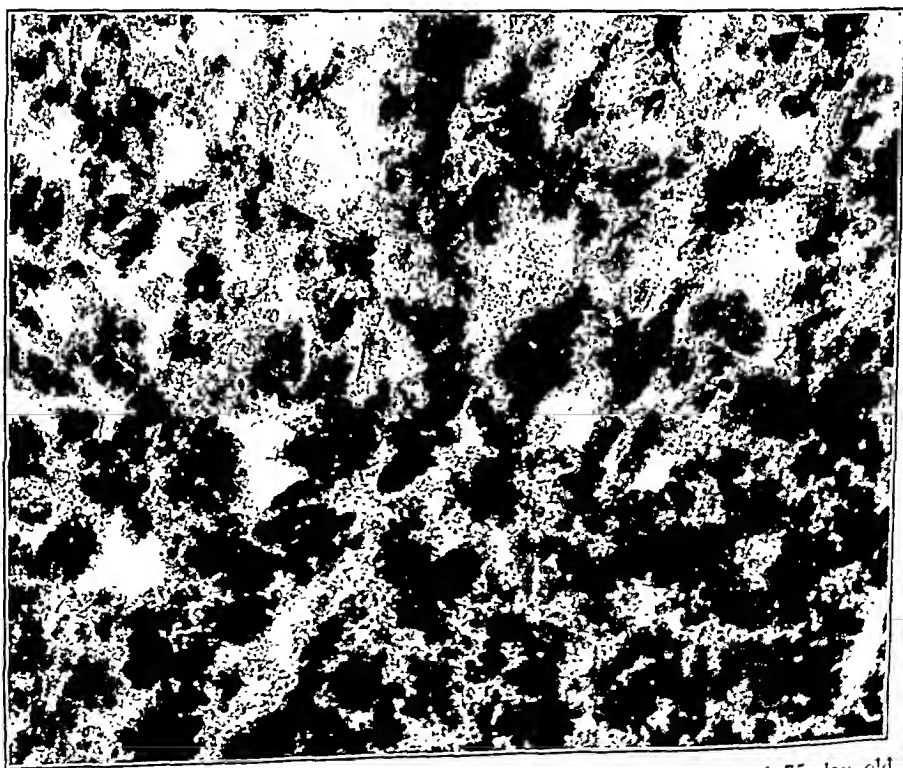


Fig. 3.—Whole mount ( $\times 18$ ) of a mammary gland of a normal 75 day old male rat, showing the characteristic dense structure made up of lobule-like acinar clumps.

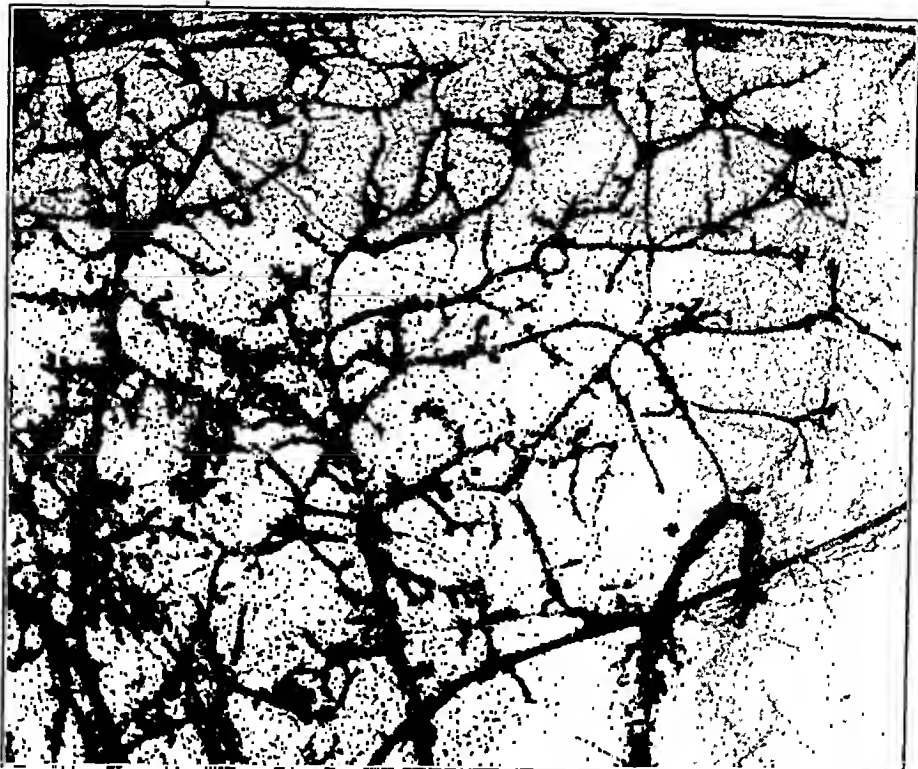


Fig. 4.—Whole mount ( $\times 18$ ) of a mammary gland of a 75 day old female rat whose ovaries were removed at the age of 21 days. The ducts are fine and bare and do not show the profusion of fine twigs and buds which result from ovarian maturation, as seen in figure 1.

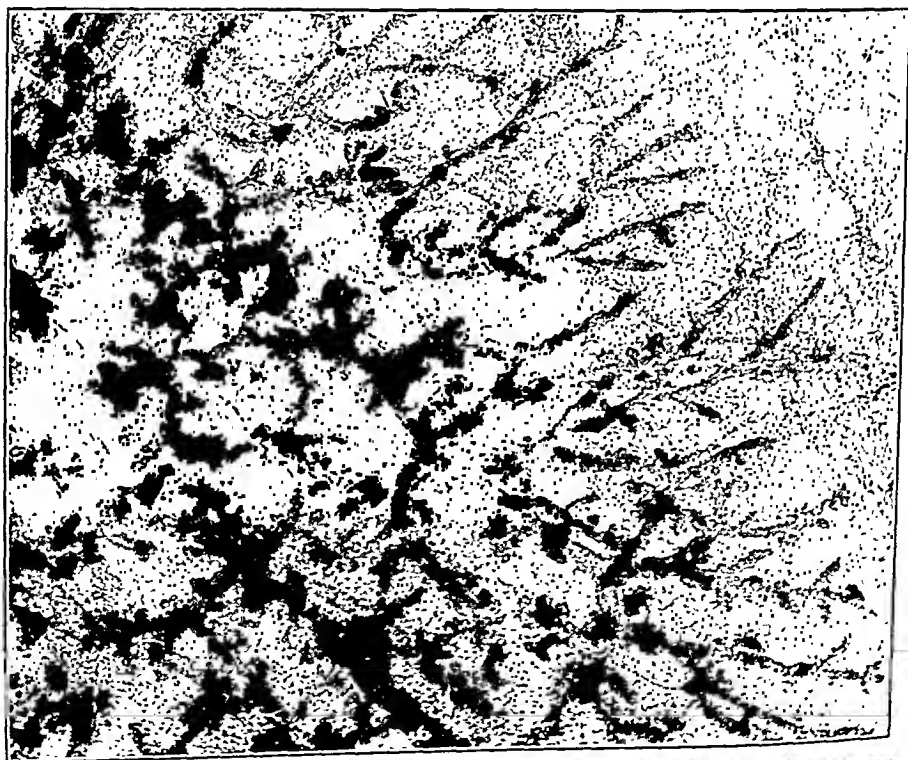


Fig. 5.—Whole mount ( $\times 18$ ) of a mammary gland of a 75 day old male rat castrated at the age of 21 days. The ducts are wider and possess more clublike branches and buds than those of the castrated female shown in figure 2. The dense growth of lobule-like structures due to testicular influence is not present. Compare with figure 3.

Giving more than the physiologic dose of estrogen or prolonging administration results in certain constant and definite abnormalities. These are probably due not to a direct action of estrogen but rather to a profound upset in the endocrine mechanism which controls mammary growth. Large doses of estrogen show their earliest effects in causing a stunted type of growth. The duct tree is less extended than with small doses and becomes more irregular; the ducts are distorted and widened, with irregular club-shaped twigs along their length. From the first there is evidence of excessive epithelial growth, especially in the

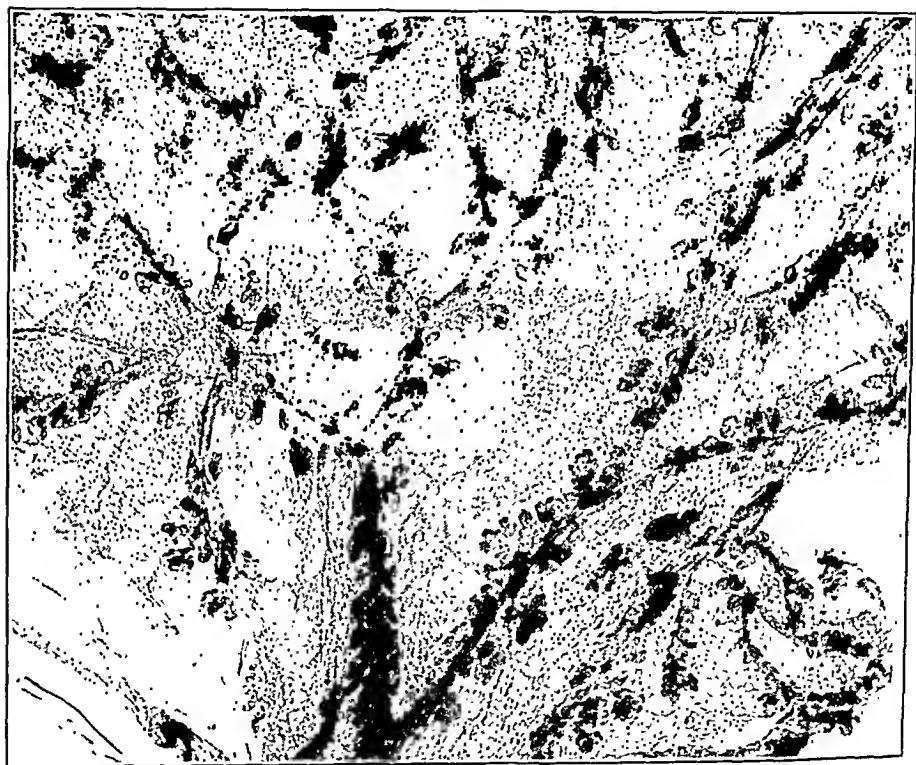


Fig. 6.—Whole mount ( $\times 18$ ) of a mammary gland of a female rat castrated at the age of 21 days and treated for nine days with 100 micrograms of estrone daily, showing the earliest effect of high doses of estrogen. The ducts are widened, and there is excessive proliferation of buds and short branches. The gland was restricted in area.

terminal buds and smaller twigs, and accompanying this growth there appears evidence of secretory activity. Figure 6 shows the breast of a rat castrated at the age of 21 days and treated for nine days with 100 micrograms of estrone daily; the widening of the short, irregular ducts and the accumulation of budlike projections can be seen. This early dwarfing can be readily accentuated by more vigorous treatment; it is distinctly pathologic.

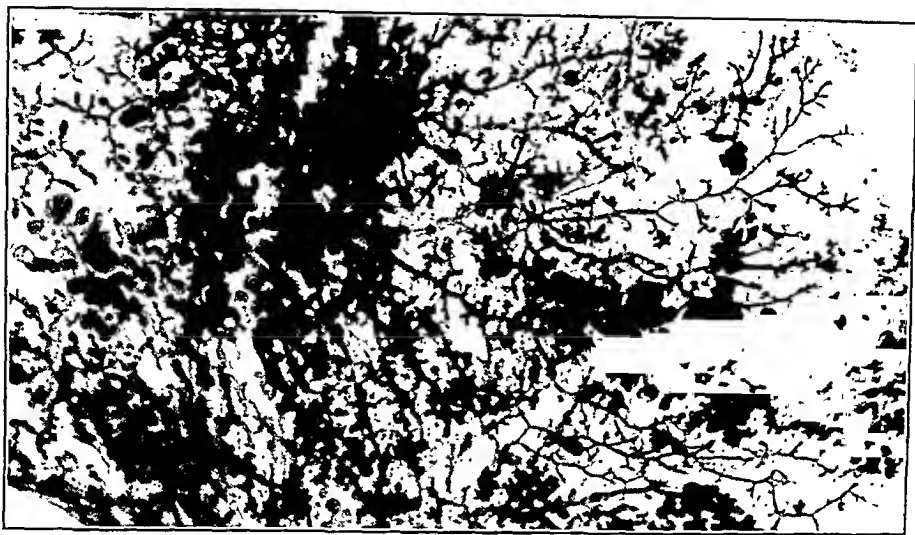


Fig. 9.—Whole mount ( $\times 3$ ) of a mammary gland of a rat castrated at the age of 21 days and given 50 micrograms of estrone daily for one hundred and ninety-three days, showing the formation of small cystic dilations and irregular epithelial buds resulting from prolonged dosage with moderate amounts of estrogen.



Fig. 10.—Paraffin section ( $\times 27$ ) of a portion of the mammary gland shown in figure 8. In this area the small cysts are nearly filled with epithelial growth and small papillomas. The picture is not unlike that of Schimmelbusch's disease in human beings.



of this cystic change. It can be seen that the smaller cysts are lined by a single layer of epithelium and that their lumens, filled with dense secretion, are in direct communication with the ducts, which are distended with a like secretion. In some areas, after prolonged overstimulation with estrogen, there is excessive epithelial growth in the ducts and in the cyst walls, resulting in a heaping up of cells and papillomatous growths (fig. 10). As the cysts become larger and older they lose their epithelial lining, and the enveloping fibrous tissue becomes more dense, surrounding the cavity as a thick wall. At this stage the original communication of the cyst cavity with the lumen of the duct is lost, and the contents can no longer be expressed without rupture of the cyst wall. Some of the cysts show excessive proliferation of fibrous tissue in their walls, while invasion of the lumen by fibroblasts gives the appearance of organization of the contained secretion (fig. 11). These cystic changes have been constantly observed in all animals receiving 100 or more micrograms of estrone daily for periods of three weeks or more, and in those animals given 50 micrograms daily for longer periods, in which they occur less often or are smaller. It has been found that the higher the dose, the more quickly the cysts develop, and the more marked is the degree of abnormal change. In animals receiving these large doses of estrogen the cystic changes can be prevented, as will be seen later, by administering other hormones.

Smaller doses of estrone given over long periods result in a different type of mammary change. Doses such as 25 micrograms daily or 100 to 200 micrograms *weekly* produce a primary stimulation of development of duct and terminal tubules marked by evidence of excessive epithelial growth. Secretory phenomena are minimal; only after long periods of treatment are cystic dilatations noted, and even then they are not marked. Instead, the primary picture of estrogenic stimulation gradually gives way to the appearance of regressive changes. The mammary gland becomes more and more varied in its architecture, and the differences noted in different regions of the normal gland are greatly accentuated. Certain regions show marked involution, with narrow, crooked bare ducts; in other regions the ducts are distended with clear secretion, and their budlike projections are dilated into microscopic cysts. Scattered throughout most of the gland are isolated areas of terminal tubular proliferation resulting in clumps of imperfectly formed lobules; occasionally one or two normal-appearing lobules made up of discrete alveoli are seen. Figure 12 shows an area of excessive epithelial proliferation in a castrated female rat treated from the twenty-

cysts, areas of epithelial proliferation and adenoma-like formation in a rat treated for six months with 50 micrograms of estrogen daily.

The changes which follow the administration of various amounts of estrogen are similar to that group of conditions in the human breast included in the term chronic mastitis. The pathologic changes of these diseases of the breast are extremely varied, but there is reason to believe that they are all attributable to a single mechanism, and for the most part the individual changes are but different degrees and different stages of the same abnormal process. Although proof is lacking, it would



Fig. 13.—Paraffin section ( $\times 27$ ) of a mammary gland of a female rat castrated at the age of 21 days and given 50 micrograms of estrogen daily for one hundred and eighty-five days. In this area can be seen dilatation of the ducts, with increased periductal connective tissue, cystic formation, excessive intracystic epithelial proliferation and an area of adenomatous growth.

appear that the formation of large cysts in the breasts of rats given more than 100 micrograms of estrone daily for several months is analogous to that form of cystic disease characterized by the presence of a limited number of large cysts (the blue-domed cyst of Bloodgood). In this condition there is little formation of lobules, and a minimum of epithelial proliferation occurs.

Those histologic changes in the breast of the rat which result from the administration of estrogen for longer periods, i. e., for six months or more, in smaller doses closely resemble the more diffuse mammary

the form of chronic cystic mastitis first described by Schimmelbusch, in which the small mammary gland with its short ducts shows extensive epithelial overgrowth, formation of adenomas and papillomas being concurrent with the cystic change. It must be remembered, however, that in the human being there is a difference in response to estrogen on the part of the fibrous stroma and of the lobular epithelium. The lobular growth, as demonstrated in the monkey, may respond more readily to stimulation by the corpus luteum hormone. Therefore, too close a parallel cannot be drawn between the mammary changes in the human being and those experimentally induced in rats.

#### EFFECTS OF STIMULATING THE GONADS

In contrast to the extension of the duct tree produced by the action of estrogen on the breast, the effect of gonadotropic substances on the intact female is the occurrence of the true changes of pregnancy, with formation of lobules. When the gonadotropic substance from the urine of pregnant women or the gonad-stimulating substance of urine taken from women after the menopause is administered to the rat, marked ovarian enlargement resulting from the formation of numerous large corpora lutea occurs. The mammary glands of animals whose ovaries are thus stimulated are indistinguishable from those of a pregnant animal at full term. Continuation of such treatment will not maintain the mammary gland in such a condition for long periods, for after a month or two the animal becomes refractory to the injected substance, the ovaries decrease in size and the mammary glands regress. The degree to which regression occurs varies greatly in different animals and with different gonadotropic preparations. In most cases involution begins between the first and the second month of injection and slowly continues for a month or more. In some cases the involuted gland is scarcely distinguishable from that of the normal, nontreated animal, but usually there is notable increase in the periductal connective tissue, and frequently there are residual areas of incomplete regression. Figure 15 shows the residual increase in connective tissue after prolonged administration of gonadotropic substance. Sometimes incompletely involuted areas stand out in contrast to the surrounding structures and may be confused with true adenoma or fibro-adenoma.

It is interesting that in animals whose mammary glands are maintained in a state similar to that of pregnancy high doses of estrogen do not produce cystic changes. As has been shown, a daily dose of 100 micrograms or more of estrone resulted in formation of cysts within three weeks in every case. When noncastrated animals are given gonadotropic substances during the period of administration of estrogen, the mammary glands show lobular development and the full changes of preg-

The herpes had improved promptly, and he had not had any untoward effects or symptoms in connection with the treatment. His history was otherwise unimportant.

The data obtained from examination did not suggest that the patient was very ill. He complained of pain in his abdomen, but it did not seem to be severe. Except in the abdomen, little of an abnormal nature was observed. The rectal temperature was 99.8 F.; the pulse and respiratory rates, normal. The blood pressure was not recorded. The abdomen was slightly distended and a little tender throughout, though there was no spasm of the muscles. No masses were palpable, and no signs of fluid were present. Examinations in the laboratory did not reveal any abnormalities. The hemoglobin content was 80 per cent (Dare), the erythrocyte count 4,020,000, the leukocyte count 8,200 and the differential count normal. The urine contained no abnormal constituents, and the Wassermann and Kahn reactions of the blood were negative.

*Instances of Intra-Abdominal Apoplexy Recorded in the Literature*

No.	Year	Author	Sex	Age	Data			
					Anatomic Location	Operation	Result	Autopsy
1	1913	Florence and Ducuing..	F	..	Sup. mesent. art.	No	Died	Yes
2	1918	Hilliard.....	M	48	Transv. mesocolon	Yes	Died	No
3	1923	Starcke.....	M	60	Gast.-duod. art.	Yes	Recovered	No
4	1925	Budde.....	M	27	L. gast.-epip. art.	Yes	Recovered	No
5	1931	Green and Powers.....	F	54	L. gast. art.	Yes	Recovered	No
6	1933	Mourgue - Molines and Cabanac	M	56	L. gast. art.	Yes	Recovered	No
7	1933	Mourgue - Molines and Cabanac	..	..	L. gast. art.	Yes	Recovered	No
8	1933	Mourgue - Molines and Cabanac (Rud)	F	73	L. gast.-epip. art.	Yes	Died	Yes
9	1935	Thompson and Dunphy	F	62	L. gast. art.	Yes	Recovered	No
10	1935	Buehlinder and Greene	M	57	R. gast. art.	Yes	Recovered	No
11	1936	Moorehead and Mc Lester	M	44	R. and l. gast. art.	No	Died	Yes
12	1936	Moorehead and Mc Lester	M	50	Sup. mesent. art.	No	Died	Yes
13	1938	Morton	M	72	Sup. mesent. art.	Yes	Recovered	No

During two days in the hospital, the patient's symptoms gradually subsided, and the distention and tenderness in the abdomen disappeared almost entirely. The tenderness, however, persisted to a slight degree, in the lower part of the abdomen on the right side more than elsewhere. It was therefore thought that the patient might have had a mild attack of appendicitis, although a positive diagnosis was not made at that time. Accordingly, when he was discharged, he was advised to restrict his diet somewhat, to avoid the use of laxatives and to report immediately if the symptoms reappeared.

Nothing further was heard from him until five days later, March 30. His wife telephoned early in the morning to relate that he had been awakened by severe cramps in the abdomen. He was at once readmitted to the hospital. Before coming to the hospital, however, he had taken an enema that had not been effectual or relieved the pain. He had been nauseated and had vomited. The results of examination at the time of readmission were essentially the same as those at the time of the former admission. There was, however, a little more tenderness throughout the abdomen, and in addition there was an indefinite mass to the left of the umbilicus. The patient's temperature was 100 F., and his pulse and respiratory rates were only slightly elevated. It was thought that he probably had an abscess in the left side of the abdomen, possibly the result of diverticulitis.

in the cases previously reported but not the highest on record, for the patient in 1 case was a year older. As for incidence in the sexes, occurrence in men seems to predominate over that in women by a ratio of 2 to 1. As in all except 3 of the other cases, the diagnosis was made in the course of operation. It is interesting that the correct diagnosis has not been made before operation in a single instance. In the 3 cases in which an operation was not performed, the diagnosis was not made prior to necropsy. In each case in which an operation was performed, the preoperative diagnosis was that of some acute abdominal emergency, such as perforated viscus, acute inflammatory process or acute intestinal obstruction. Of the conditions mentioned as tentative preoperative diagnoses, that most nearly related to the true condition was mesenteric thrombosis. Probably the most interesting fact about abdominal apoplexy is that, in spite of its similarity to cerebral apoplexy, a condition frequently encountered, it has rarely been observed. Of course, it may occur much more frequently than published reports would indicate; nevertheless, even though allowance is made for this discrepancy, the condition must still be rare in comparison with the incidence which might be expected.

The reported cases were almost all those of persons in the period of life in which arteriosclerosis is always present to some degree. In cases in which tissue was examined there was both gross and microscopic evidence of arteriosclerosis. There would seem to be no doubt, therefore, that arteriosclerosis is the underlying pathologic process usually responsible for the rupture of the vessel and the consequent hemorrhage. The precipitating cause of the rupture may be, as in the case of cerebral hemorrhage, unexplainable. Anything that raises blood pressure might well predispose to a blowing out at any previously weakened spot. In the case here reported a pressor drug had been administered hypodermically a few days before the first abdominal symptoms appeared. It seems fair to assume that this drug may have played a part in the rupture of the vessel. On the other hand, it is not uncommon for cerebral hemorrhage to occur while one is asleep, although blood pressure is then presumably at its lowest and most stable level. If one may reason by analogy, one may conclude that there need not be any precipitating cause for the hemorrhage. The vessel wall in a diseased area merely becomes gradually too weak to withstand even normal systolic pressure and finally ruptures. All these considerations still leave unexplained the rarity of intra-abdominal apoplexy.

Spontaneous rupture of an aneurysm within the abdominal cavity is an accident that is pathologically and clinically related to intra-abdominal apoplexy. It occurs much more frequently, however, perhaps because of the difference in effective pressures in the larger and the smaller vessel, and is usually immediately fatal. Instances of rupture of aneurysm of the aorta are not uncommon, and the same is true to a

are unexplained. The condition does not seem to have any distinctive characteristics that may lead to a positive diagnosis. It should, however, be thought of as a possibility in any case in which there are signs of peritoneal irritation. Treatment is surgical and should be by ligation of the bleeding vessel whenever practicable.

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appendectomies performed for acute appendicitis; the diagnosis was verified by the pathologist in each case. Study of the 751 histories emphasizes the frequently bizarre nature of the early signs and symptoms presented by patients with acute retrocecal appendicitis.

Four hundred and seventy-one (62.72 per cent) of the patients were men. Krasnoselskiy stated the accepted opinion that the incidence of acute appendicitis is less in women, that the condition runs a milder clinical course, and that the mortality is about one third of that occurring in men. Table 2 supports this contention. The average age of the 751

TABLE 2.—*Mortality and Distribution of Diseased Appendixes According to Sex*

Author	Year	Number of Cases	Males				Females			
			Cases		Deaths		Cases		Deaths	
			Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Finney.....	1933	1,807	1,111	61.5	65	5.85	696	38.5	24	3.45
Werill and Wallace...	1934	8,265	4,652	56.2	241	5.2	3,613	43.8	129	3.6
Lamon.....	1936	206	.....	.....	8	.....	.....	.....	6	.....
Boyce and others.....	1936	2,715	1,848	68.0	106	5.7	867	32.0	51	5.9
Collins.....	1938	751	471	62.72	41	8.7	280	37.28	17	6.07

TABLE 3.—*Distribution of Diseased Appendixes by Age Group, Expressed in Percentage*

Author	Year	No. of Cases	Age Groups by Years								
			0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	80+
Pattison.....	1936	1,211	10.47	38.3	29.1	10.0	5.78	3.55	1.73	0.33	0.08
Reid and others....	1936	3,100	6.6	28.3	36.4	18.7	5.78	2.81	1.1	0.29	0.00
Pool.....	1936	757	10.7	41.3	27.7	13.4	4.35	2.11	0.26	0.00	0.00
Rhodes and others..	1936	1,000	8.3	32.7	30.7	13.4	8.3	3.6	1.9	0.3	0.2
		6,668									
Average percentage.....			9.02	35.15	30.97	13.9	6.05	3.02	1.25	0.31	0.14
Collins.....	1938	751	6.25	15.16	40.43	21.55	9.44	4.25	2.13	0.66	0.60

persons was 29.7 years. This age is higher than that usually reported for acute appendicitis. Three hundred and four instances (40.48 per cent) occurred in the third decade of life. There is a noticeable increase in the incidence of this type of appendicitis in the later decades, as depicted in table 3.

Racial and seasonal incidence showed no noteworthy features. The various occupations and previous residences of these persons were unimportant in respect to this study. Interestingly, 267 persons (35.55 per cent) presented histories of other members of their families having suffered attacks of appendicitis that necessitated surgical intervention.

The past histories of these persons were of great importance. Three hundred and one (40.08 per cent) mentioned the previous frequent occurrence of infections of the upper part of the respiratory tract, and in

Of the 280 women of this series, 44 (5.86 per cent) had received medical treatment for pelvic inflammatory disease, without obtaining noticeable relief. At the time of the appendectomy, 33 (4.394 per cent) showed no evidence of the previous existence of any pelvic inflammatory disease. Two (0.27 per cent) nephropexies had been performed in the past for conditions in the right side of the abdomen, without relieving the patients. Forty-five women (5.99 per cent) had been subjected to various gynecologic procedures, without experiencing permanent relief. An additional 31 (4.13 per cent) had had major pelvic operations of various types, at which, for one reason or another, their appendixes had not been removed.

There were thus 147 persons (19.57 per cent) whose abdomens had been opened previously for other suspected intra-abdominal diseases, but during these operations their appendixes had not been removed, and they subsequently suffered attacks of acute appendicitis. Therefore, most of these persons had been subjected to needless secondary operations, at a time when the operative risk and the postoperative morbidity were greatly increased. Most regrettable was the fact that 6 (0.80 per cent) died. Of the 141 patients (18.77 per cent) with histories of previous abdominal explorations who survived, 131 (92.91 per cent) were relieved of their persistent complaints. Thus, 56.99 per cent of this entire series of 751 patients had received treatment in the past for diseases of the gallbladder, the pyloric region, the pelvis or the right part of the genitourinary tract. Gynecologic operations were the vogue among the 280 women of this series, while operations on the upper part of the abdomen were fashionable among the 471 men.

Nausea, headache, flatulence, heartburn, regurgitation, insomnia, constipation and lack of appetite, of which many of these patients complained, disappeared in 73.4 per cent of the cases after appendectomies. Distress following the ingestion of cheese, rich or greasy fried foods and raw fruits likewise frequently vanished after the removal of the diseased appendixes. Many persons who complained of symptoms simulating either cholecystitis or peptic ulcer were either cured or greatly relieved after appendectomies. In 12 (1.60 per cent) persons over 55, certain long-continued arthritic pains disappeared after the removal of their appendixes. In 21 persons (2.80 per cent) of the same age group, similar symptoms were greatly diminished by appendectomies, which appreciably increased their usefulness both to themselves and to others.

One hundred and thirty-seven patients (18.24 per cent) complained of mild pains of several days' duration in the epigastric or the right hypochondriac region, which failed to become localized at McBurney's (or more properly, McArthur's) point in the right lower quadrant of the abdomen. Two hundred and fourteen persons (28.50 per cent)



The average leukocyte count in this series was 11,870 cells per cubic millimeter of whole blood, with an average differential count of 83.0 per cent of polymorphonuclear neutrophils. Thus, the blood showed a slighter leukocytosis than is usually present in cases of acute appendicitis. Interestingly, the urine of 104 patients (13.85 per cent) contained an appreciable number of erythrocytes, while pyuria was recorded in 152 histories (20.24 per cent), evidence being present in even the catheterized samples. Such urinary observations often were misleading and usually caused operative delay until diagnostic procedures could be utilized to rule out the existence of disease in the right part of the genitourinary system. These patients when operated on later frequently revealed an acutely inflamed appendix lying across the course of the right ureter, with an accompanying secondary acute periureteritis. For 37 women (4.93 per cent) sedimentation rates were determined in an effort to rule out the possible existence of pelvic inflammatory disease. In only 3 instances (0.4 per cent) were the rates abnormal. These observations thus agree with those previously made by Lesser and Goldberger that the sedimentation rate for women suffering from acute appendicitis is normal. (See table 5 for further details.)

Correct preoperative diagnoses of acute appendicitis were made in only 554 cases (73.77 per cent). In the recent study by Rhodes, 75 of his preoperative diagnoses were tabulated as follows: correctness on the question of perforation in 58.6 per cent of the instances, on the question of the location of the appendix in 40.0 per cent and on the question of local pathologic changes in 33.3 per cent. In 136 persons (18.11 per cent) erroneous preoperative diagnoses were made of acute perforated peptic ulcer. In 53 additional persons (7.06 per cent) preoperative diagnoses were made of acute empyema of the gallbladder with impending perforation. Five persons (0.67 per cent) were considered to have acute pancreatitis. Three patients (0.40 per cent) were decided to be suffering from acute mesenteric vascular occlusions.

Of the 554 cases (73.77 per cent) in which correct preoperative diagnoses of acute appendicitis were made, only 304 (40.48 per cent) were correctly diagnosed as of the retrocecal variety. In these 304 cases, as a result of such preoperative diagnoses, 277 (36.88 per cent) lateral and cephalad placed muscle-splitting incisions (rather than the usual McBurney incisions) were made in the right lateral anterior abdominal wall. This type of incision gave an excellent exposure of the retrocecal region and permitted the performance of appendectomy under direct vision, the latter point being a most important factor in lessening postoperative morbidity. (See table 6 for further information.) No herniations occurred postoperatively with this type of muscle-splitting incision. The period of hospitalization of these patients was on

an average 9 days shorter and only one-eighth as many postoperative complications occurred among them as among those having had either midright rectus or midline incisions. Consult table 6.

However, in instances in which a doubt existed as to the cause of the acute condition in the abdomen, preliminary exploratory midright rectus incisions were made at the level of the umbilicus, so that they could be extended either caudally or cephalically as the intra-abdominal observations dictated. In 77 patients (10.25 per cent) walled-off retrocecal abscesses were palpated through such exploratory incisions. These

TABLE 7.—*Tabulation of Postoperative Complications in This and Other Series of Cases of Acute Appendicitis*

Postoperative Complications	Author and Number of Cases Reported				
	Boland, 4,270	Weyll and Wallace, 8,265	Pattison, 1,148	Sperling and Myrick, 433	Collins, 751
Ileus.....	33	..	..	..	23
Fecal fistula.....	7	59	..	..	2
Enterostomy.....	18	50	9	..	6
Bronchitis.....	..	150	..	..	50
Bronchopneumonia.....	12	19	7	..	58
Lobar pneumonia.....	0	46	..	..	10
Pulmonary atelectasis.....	..	13	..	..	19
Pulmonary embolism.....	2	8	..	..	0
Empyema.....	1	8	..	..	4
Cardiac disease.....	3	..	..	..	19
Peritonitis.....	335	1,274	129	68	161
Pleurisy.....	..	18	..	..	22
Lung abscess.....	..	1	..	..	6
Infected incision.....	..	234	67	22	93
Incomplete intestinal obstruction.....	..	56	..	..	14
Acute intestinal obstruction.....	..	67	9	5	22
Peritonitis with obstruction.....	..	22	..	..	9
Subdiaphragmatic abscess.....	..	17	2	..	11
Subhepatic abscess.....	..	..	2	..	7
Thrombosis and phlebitis.....	..	32	..	..	26
Pelvic abscess.....	..	30	41	..	97
Intra-abdominal abscess.....	..	23	11	..	31
Appendical abscess.....	197	1,123	268	107	234

were then closed without disturbing the abscesses and secondary muscle-splitting incisions were made directly over the abscesses and proper drainage instituted.

In the remaining 474 cases (63.12 per cent), in which either midright rectus incisions (313—[41.68 per cent]) or midline incisions (161—[21.44 per cent]) were employed, the appendixes were removed usually through lengthened incisions with considerable difficulty. This necessitated increased retraction of the edges of the wound, with a resultant increased degree of trauma to the anterior abdominal wall. Thirty-one (4.12 per cent) such incisions required a secondary closure before the patients could be dismissed from the hospital. In 51 additional cases (6.79 per cent) hernias of varying degree developed after incision. There were 319 examples (42.48 per cent) of troublesome complications

Twelve (1.60 per cent) of the 97 patients with pelvic abscesses died; 10 (1.33 per cent) of these deaths were attributable to the non-muscle-splitting incisions. These pelvic abscesses, after their localization, were

TABLE 11.—*Percentage of Mortality per Age Group Compared With Previously Reported Series*

Age Groups (in Years)	Percentage of Mortality per Age Group	
	Average of 21,289 Cases Reported by Various Authors* Between the Years of 1931-1936	Collins, 1933, 751 Cases
1-10.....	10.6	10.8
11-20.....	2.66	4.3
21-30.....	4.0	4.3
31-40.....	6.7	4.9
41-50.....	11.14	14.1
51-60.....	11.70	25.0
61-70.....	21.65	50.0
71-80.....	57.2	40.0
81-90.....	100.0	....

\* Bower (in 1931); Wevill and Wallace; Pattison; Pool; Boyce and McFetridge, and Rhodes, Birnbaum and Brown.

TABLE 12.—*Relationship of Duration of Symptoms Before Operation With Percentage of Mortality in Acute Appendicitis; Comparison of This Series With Others*

Time in Hours	Author, Year and Number of Cases Reported					
	Bower, 1931, 5,121	Boland, 1932, 4,270	Maes and Others, 1935, 2,295	Pattison, 1936, 1,166	Boyce and Others, 1936, 2,715	Collins, 1933, 751
0-6.....	2.55	0.00	2.0	0.00	1.6	1.7
7-12.....		1.00				0.0
13-24.....		2.32				3.5
25-48.....	6.31	6.45	4.6	5.60	4.8	5.9
49-72.....	8.59	6.50	7.5		6.8	7.3
Over 72.....	11.83	8.00	12.3		15.7	13.2

TABLE 13.—*Mortality for the Surgical Treatment of Acute Appendicitis*

Author and Year	Total Cases	Total Deaths	Average Mortality, Percentage
Various authors,* 1931 to 1937.....	60,130	3,046	5.06
Collins, 1933.....	751	55	7.14

\* Bower; Boland; Finney; Keyes; Reid; Wevill and Wallace; Stanton; Harris; Cayford; Lied; Black; Merrell; Kline; Eiken; Maes and McFetridge; Krasvoselskiy; Greiner; Schroder and Steinel; Lamon; Liveland; Hobler; Reid; Poer and Merrell; Nuzum; Pattison; Cook and Beardsley; Pool; Boyce and McFetridge; Rhodes, Birnbaum and Brown; Jensenius; Spærling and Myrick, and Holder and Wells.

drained, wherever possible, either through the anterior rectal wall in men or through Douglas' cul-de-sac in women. No permanent fistulas resulted from such methods of drainage, and none of the patients died.

Eleven instances (1.46 per cent) of subdiaphragmatic abscesses were encountered and 4 of the patients affected died. There were 8 patients

previous contentions of Bower as to the deadliness of preoperative catharsis in instances of acute appendicitis.

Some of the important features of the operative technic were briefly as follows: Less attention was paid to the day of the disease than to the condition of the patient. If the patient was growing steadily worse, exploration was usually believed to be indicated. If, on the other hand, the patient had a palpable mass in the lower part of the abdomen and was improving, surgical intervention was not employed at that time. Spinal anesthesia was used routinely unless some condition was present in the patient that served as a definite contraindication to its use. Every possible effort was made to drain extraperitoneally localized appendical abscesses, but such abscesses were never drained across the clean peritoneal cavity. Only localized appendical abscesses were drained by the use of simple Penrose drains constructed from rubber dam material.

If the appendix formed part of the wall of an abscess, if its removal would lead to the extensive breaking down of protective adhesions or if the patient was a poor risk, operative time was not wasted, nor was the life of the patient placed in additional jeopardy by foolish insistence on the completion of a difficult appendectomy. In such cases the patients were asked to return to the hospital for the performance of an interval appendectomy 10 weeks after their dismissal. All pelvic abscesses were drained, if possible, through either Douglas' cul-de-sac or the anterior rectal wall. The stump of the appendix was not inverted, and no reason has been encountered to regret the use of this simpler technic. I employ muscle-splitting incisions as a matter of routine whenever possible, because I believe that the use of such incisions insures a definite lowering of both the operative mortality and the postoperative morbidity. In no instance was a tight reapproximation of the edges of the skin permitted. Skin clips were used by preference. At the first sign of infection of the wound, adequate through and through drainage was instituted, both to hasten the final healing of the incision and to prevent the onset of extensive phlegmons of the anterior abdominal wall, which are often of anaerobic origin.

All patients were placed in Fowler's position postoperatively, and the principles of Ochsner were closely followed. Nothing was given by mouth until flatus was passed, abdominal distention had disappeared and the temperature had fallen toward normal. In the interim, fluids were usually administered by hypodermoclysis, or, if necessary, by the intravenous route, usually in daily amounts of 2,000 cc. No patient was allowed to be out of bed until the incision was healed and the temperature had been afebrile for 4 days. Before dismissal from the hospital, a rectal examination was mandatory to exclude the possibility of the

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## FRESH FRACTURE OF THE OS CALCIS

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A broken leg as a rule causes too great a disability to allow a mistaken diagnosis. Not so with many fresh fractures of the os calcis. If the damage is severe enough the physician's attention is focused and his diagnostic curiosity challenged to the point that early roentgenograms are generally taken. Thus, a "sprain" turns out to be a crushing fracture of the heel bone. Too often, even in the larger centers, the ancient empirical form of treatment, consisting of "rest in an encasement until consolidation has arrived," is applied. I wish to advocate, briefly, a manner of treating fresh fracture of the os calcis by closed reduction, modeling the fragments by force and encasing the restored foot until healing takes place.

### HISTORICAL TREATMENT

In 1720 Garangeot, of France, first described accurately the "smash fracture." Petit and Desault, his countrymen, reported their cases in the same year and advised "rest until fragments had consolidated." Bilgner, of Germany, in 1720 added to the literature a good clinical description of the injury. For one hundred years no one propounded any change in the treatment, though a number of papers were published. The surgeon of that time appeared contented to describe in great detail every clinical variation of the condition and was not much interested in treatment. Cooper, in England, in 1835 recommended dressings of egg albumin and cotton lint unless the extremity appeared gangrenous; if it was gangrenous he amputated. Pott sawed off the ends of the bone in all cases of compound fracture to prevent tetanus and so, of course, sawed away the heel bone when it was badly damaged. Mutilation and frequent deaths followed, as may be imagined. In 1839 Norris, the first American to report his results, followed the same rugged form of treatment. The first classic description and discussion of the mechanics involved in the production of this type of fracture were written by Nadal and Malgaigne in 1843, in Paris. Bérard in 1845, Bauchet in 1853 and Demarquay in 1854 advised the use of lint and cottage cheese encasement.

Clark, an American, in 1855 applied traction to the posterior fragment by means of a pulley apparatus; the exact method is not clear from his writings. He then used gutta-percha splints. Every one feared the

modified the method by substituting tenotomy of the achilles tendon. Cotton in 1921, in another classic, using freehand drawings from his notebook, a form of illustration which always enlivens an otherwise staid manuscript, expressed the opinion that impaction is not altogether sound mechanically and directed attention toward the remodeling of fragments as perhaps the most important step. He said that in all cases arthrodesis is distinctly inadvisable and that he preferred to break up adhesions in the subastragalar joint and restore lateral mobility. He then permitted weight bearing after the eighth week.

The following outline, illustrated in figures 1 and 2, is a review of the manifold ways of treating fractures of the os calcis.

#### 1905

Eisendrath: open reduction, fixation with kangaroo tendon, cast.

#### 1908

Cotton and Wilson: closed reduction after breaking up of impaction with a mallet, traction on the achilles tendon, reimpaction, cast with felt pads beneath malleoli for compression and under longitudinal arch of foot.

#### 1912

Van Stockum: open reduction with subastragalar arthrodesis, cast.

#### 1913

Drewke: open reduction, cast.

Gelinsky: closed reduction, drill fixation from without, cast.

Leriche: open reduction, bone plates, steel screws for fixation, cast.

Soubeyran and Rives: primary astragalectomy.

#### 1916

Lounsbury: Cotton's technic, occasionally open reduction, fixation with kangaroo tendon, tenotomy, cast.

Forrester: manual manipulation, tenotomy, cast (with the foot in plantar flexion over a roller bandage and the heel well down), fixation with kangaroo tendon if necessary.

#### 1917

Bendixen: Cotton's technic, carpenter's clamp or fixation with kangaroo tendon, cast.

Cahill: Cotton's technic or fixation with nail, cast.

Magnuson: essentially Cotton's technic plus tenotomy, cast, then special shoe.

#### 1918

Whiteside: open reduction, fixation with silver wire, tenotomy, cast.

#### 1919

Davis: Cotton's technic.

#### 1920

Foldes: Fischer's leaf spring apparatus for external traction for reduction and maintenance, pin through posterior fragment.

Mumford: essentially Cotton's technic, with reduction leverage over iron pipe and tenotomy.

Magnuson: former technic plus reduction leverage over wedge, cast, weight bearing in eight weeks.

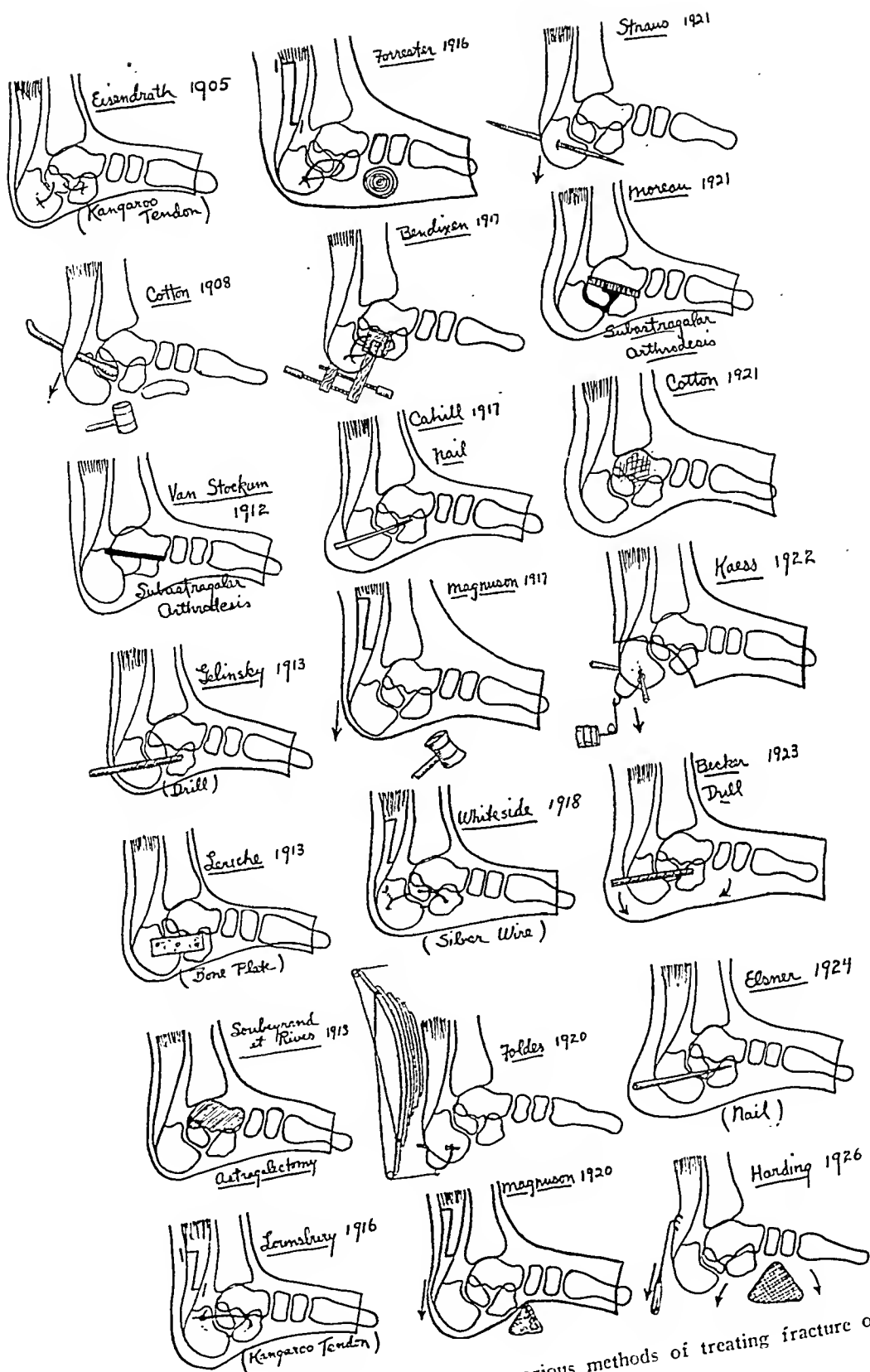


Fig. 1.—Pictorial review of the various methods of treating fracture of the os calcis.



Conn: closed reduction, wrenching of foot, tenotomy, fixation with nail, cast, occasionally subastragalar arthrodesis.

Gleich: open reduction, wedge osteotomy, cast (fresh fractures).

Bérard and Mallet-Guy: open reduction, cast.

Schnek: Böhler's technic.

Wilmoth and Lecœur: open reduction, osteoperiosteal grafts, no cast for first week, then cast for twelve weeks.

Chatterton: Cotton's technic, with tenotomy.

Oudard and Le Bourgo: closed reduction by hand, cast, occasionally open reduction with fixative material and subastragalar arthrodesis.

Simon and Stulz: open reduction, sectioning of peroneal tendons, fixation with bone plate, suture tendons, cast; sequestration frequent result.

Schwartz: open reduction, cast.

Fontoynt and Estrade: cast alone.

### 1930

Bendixen: carpenter's clamp, with two blocks for compression, plus Cotton's technic, occasionally open reduction, fixation with kangaroo tendon, cast.

Crossan: triple arthrodesis, wedge osteotomy, tenotomy, cast (old fractures).

Simon and Stulz: open reduction, subastragalar arthrodesis, with packing in of bits of fragments cut from fracture site or medial malleolus (inner incisional approach), occasionally use of bone plates, screws.

Gillette: cast from toes to groin, fenestrated heel portion, turnbuckle component embedded in cast for push on pin above os calcis, behind achilles tendon, to accomplish reduction and fixation.

Pichon: open reduction, with osteoperiosteal grafts, cast.

Dieulafe: open reduction, fixation with silver wire, cast.

Hermann: Cotton's technic.

Dachtler: special fracture, cast alone.

### 1931

Reich: traction on heel plus impaction with mallet, occasionally fixation with nail, cast.

Bartley: open reduction, double arthrodesis, fixation with bone peg, cast.

White: rapid Böhler technic with patient on Hawley table, reduction accomplished immediately, cast wedged for further correction if necessary.

Mouchet and Allard: cast alone.

Didiée: fracture of apophysis, rare, manual replacement, cast.

Monod: cast for four weeks, then double arthrodesis.

Patel, open reduction, fixation with nail, cast, spontaneous arthrodesis desired.

Wilmoth: open reduction, grafts with full thickness from shaft of tibia for fixation, cast.

Böhler: former technic.

### 1932

Harding: former technic, occasionally fixation with screw or nail.

Reich: Cotton-Funsten combination, occasionally plus Böhler's technic.

Mouchet, Allard and Mégnin: special fracture of anterior portion of large apophysis, cast alone, with foot in marked dorsiflexion.

### 1933

Pierce: Cotton's technic, occasionally subastragalar arthrodesis.

Myers: impaction allowed to remain, cast for only three weeks, early weight bearing.

per cent. The general trend appears to be in the direction of less time lost from employment and much lower percentage allowances for permanent partial disability, in spite of a contrary opinion held by most insurance carriers.

#### TREATMENT

Eight patients with fresh fracture of the os calcis were treated by immediate reduction, with gas-oxygen anesthesia and a modified carpenter's clamp described by Yergason in 1935 being used. Such a clamp can be adapted for this use by fastening to the inner surface of each jaw, near the tips, a rounded wooden block about 4 cm. in diameter.

The blocks attached to the inner surface of each jaw are applied over thin felt to the lateral and the medial sides of the heel, and the clamp is screwed down by compression. One exerts tremendous force on the

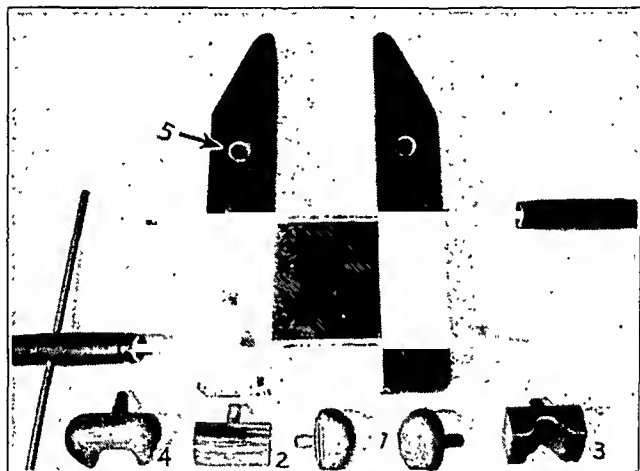


Fig. 3.—Clamp used in molding the fragments and reducing the fracture: 1, hemispherical blocks for lateral modeling; 2, oblong block used against plantar surface; 3, grooved block to fit around the attachment of the achilles tendon over the tuberosity; 4, semilunar block used beneath the lateral malleolus, and 5, holes through the jaws to carry muslin ties to hold the clamp to the foot.

fragments in this manner, loosening the clamp and shifting its jaws over the surfaces to compress and mold the heel. A crescent-shaped block, easily made in one's workshop, is then substituted for one of the rounded blocks, and the extruded fragments are pressed into the body of the os calcis by applying the jaw bearing this crescent-shaped block beneath the lateral malleolus. In this manner all medial and lateral displacements can be corrected by pressure modeling with surprisingly little difficulty.

In cases of evulsion of the upper tuberosity, or fish mouth fracture, in which a fragment is pulled upward by the achilles tendon and there is plantar displacement of other fragments, the bones are molded forcibly

always be used beneath the blocks and the muslin ties. The displaced fragments are then forced into position, and the posterior part of the os calcis is brought into normal relations with the head, so that the normal tuber joint angle is restored. This angle, described by Böhler, is made by the intersecting of a line drawn from the posterior-superior tuberosity of the os calcis to the superior-posterior portion of the astragalocalcaneal joint and a line drawn from the superior-posterior portion of the astragalocalcaneal joint and the anterior-superior projection of the head of the os calcis. This angle is normally between 25 and 35 degrees. Thus a tenotomy of the achilles tendon is unnecessary for reduction of the upper posterior fragment. This type of clamp is superior to Böhler's clamp because it permits application of much

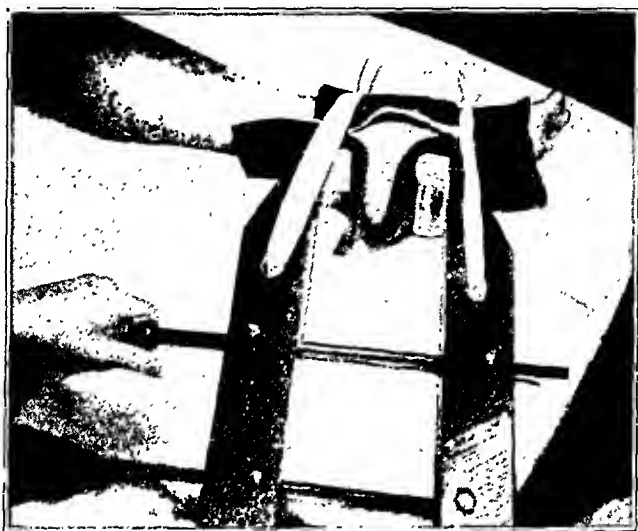


Fig. 6.—Third position, in which blocks 2 and 3 are used to bring down the posterior tuberosity and raise the head of the os calcis. The clamp cannot get away from the foot because of the muslin ties.

greater force over all surfaces and allows the heel to be drawn down immediately, removing the necessity for continued traction.

Felt padding is then applied to the sole, extending around the heel and up to the knee. A snugly fitting plaster encasement is then adjusted from the toes to the upper part of the thigh; the knee is slightly flexed, with the foot in the position caused by slight talipes equinus, and a walking iron is incorporated. Elevation is insisted on for forty-eight hours, followed by walking on crutches, with weight bearing permitted after the tenth day. At the end of the second week the encasement is cut away above the knee. The plaster is removed at the end of the tenth week and physical therapy begun. Weight bearing is allowed at the end of the twelfth week, with a longitudinal arch support, made of firm felt or metal, in the shoe.

## REPORT OF CASES

CASE 1.—P. M., a man aged 52, fell 25 feet (7.6 meters), landing obliquely on one foot and crushing completely the right os calcis; the tuber joint angle was obliterated. Reduction was accomplished by molding the posterior portion of the foot with a special clamp, and immobilization was accomplished by applying a plaster of paris encasement, which was worn for ten weeks. Weight bearing was permitted after the fourteenth week, and the injured man returned to work after the twenty-fourth week.

CASE 2.—D. P., a man aged 42, jumped from a height of 16 feet (4.9 meters), landing on a hard concrete surface and suffering a compression fracture of the



Fig. 9.—Walking cast completed and in position for drying.



Fig. 10.—Oxford worn, showing the type of leather and the longitudinal arch support of felt.

right os calcis. The tuber joint angle was obliterated, and the fragments were markedly displaced. Reduction of the fracture was accomplished by molding with special clamps while the patient was under general anesthesia. The tuber joint angle was restored, and a plaster of paris encasement incorporating a walking iron was applied. This was removed after the ninth week, and weight bearing was permitted after the eleventh week. The injured man returned to work after the thirteenth week. A spontaneous subastragalar arthrodesis materially aided his early recovery.

CASE 3.—H. B., a man aged 39, fell through the planking of a scaffold from a height of 12 feet (3.6 meters), fracturing his right os calcis. The fragments

for ten weeks. After the twelfth week weight bearing was permitted. After the sixteenth week the patient disappeared from the city, and he was not heard of for two years. When he returned he showed complete recovery of his left foot, but he had moderate postreduction traumatic arthritis of his right subastragalar joint. A double arthrodesis was done, and weight bearing was permitted after the sixteenth week. This patient is still under treatment, but a satisfactory result seems apparent.

In these cases the average age was 39 and the average fall 28 feet (8.5 meters). The patients were all men. Six of the fractures were on the right side and three on the left. The average period of disability was eighteen weeks. In five cases no percentage disability was allowed.

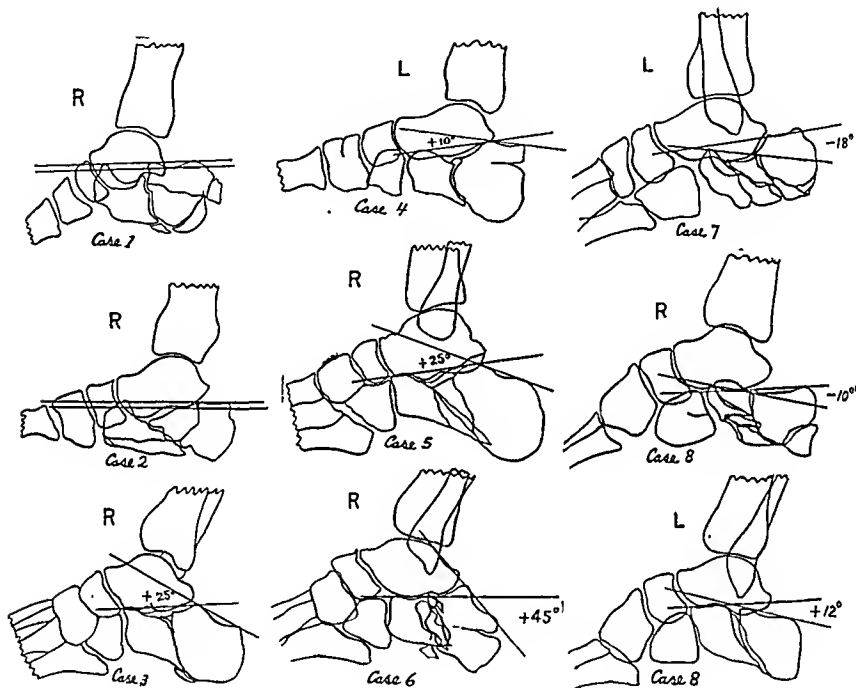


Fig. 11.—Tracings made from roentgenograms to illustrate the eight cases of fracture reported, with lines drawn to show the variety of tuber joint angles encountered.

In one case there was 10 per cent allowance and in another case 50 per cent. The treatment in one case is not completed.

#### RESULTS OF TREATMENT

Six of the 8 patients made a comparatively rapid recovery. One had post-traumatic arthritis in the subtaloid joint, refused arthrodesis and was given a 50 per cent disability allowance. The last patient disappeared for two years before treatment had been completed. When he returned his complaints were centered about the plantar surface of the

## SUMMARY

The methods reported in the literature are discussed.

A pictorial method, affording a rapid review of technic, is utilized.

According to the literature, there appears to be a tendency to discontinue the use of internal fixatives and to depend on closed reduction, forcible molding of fragments and skeletal traction. An old, painful fracture is best treated by double or triple arthrodesis.

More recent writers report shorter periods of disability.

Eight cases are reported in which closed forceful molding by means of a clamp and blocks was used.

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# COLLECTION OF AIR IN THE RIGHT SUB-DIAPHRAGMATIC SPACE

WITH SPECIAL REFERENCE TO HEPATODIAPHRAGMATIC  
INTERPOSITION OF THE COLON

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In the past decade, surgical literature has been replete with reports on eventration and on hernia of the diaphragm as well as on the role of the diaphragm in the surgical treatment of pulmonary tuberculosis, especially phrenicectomy and artificial pneumothorax. Articles in which the roentgenologic diagnosis of subphrenic abscess has been discussed are also available. There is, however, a dearth of material bearing on the significance of collections of air or gas under the diaphragm.

The presence of air in the subdiaphragmatic space is particularly pertinent when it is demonstrated roentgenologically to be on the right side, that is, between the diaphragm and the liver. In the left subphrenic area gas may be found in the cardiac end of the stomach (*Magenblase*) and in the splenic flexure of the colon, both of which lie directly beneath the leaf of the diaphragm. This is usually of no clinical importance. On the other hand, when gas or air occupies the space between the diaphragm and the liver, the finding signifies the presence of a pathologic condition or of some abnormality.

It is generally known that the right cusp of the diaphragm lies in direct contact with the superior surface, or dome, of the right lobe of the liver. During respiration in the normal state, the diaphragm and the liver move in unison. In a roentgenogram, their shadows merge and have the same density, so that one cannot be distinguished from the other. The histologic elements, such as the areolar tissue, the few blood vessels and the ligamentous attachment of the liver, that occupy the subphrenic space cast no differentiating shadows on the film. However, when this region is involved in a pathologic process, such as the presence of gas, fluid or tumefaction, which may cast a shadow of greater or less density than those of the liver and the diaphragm, or which by its presence may displace either one or both of these structures, a subdiaphragmatic lesion becomes evident in the roentgenogram. With the accumulation of air or gas in the subphrenic area, the potential space between the liver and the diaphragm becomes real. Gas is an excellent contrast medium, and by its presence the dia-

In the majority of cases, air can be demonstrated in the subdiaphragmatic space twenty-four hours or longer after an abdominal laparotomy (fig. 2). The accumulation of air may be very slight but is readily observed in the roentgenograms taken with the patient in the erect position.

#### ROENTGENOLOGIC APPEARANCE OF CONDITIONS OF AIR

When air between the diaphragm and the liver is free, it has a crescentic appearance, assuming the contour of the diaphragmatic dome above and the arch of the superior surface of the liver below. The air does not appear in the views which are taken with the patient in the prone position. However, when the patient assumes a semirecumbent or an erect posture, the air rises and collects under the diaphragm and so

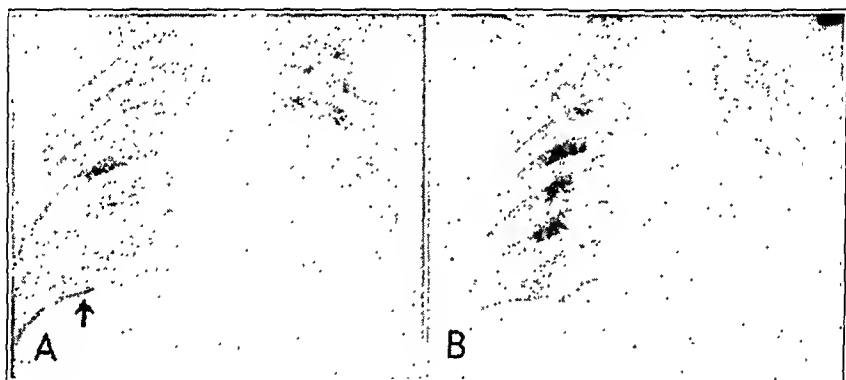


Fig. 2.—*A*, view of the chest of a patient in the erect position, taken three days after appendectomy. The presence of air between the diaphragm and the liver is clearly seen. *B*, view of the chest of the same patient in the horizontal position. The collection of air has disappeared, leaving a normal subdiaphragmatic space.

becomes visible in the film. The gas is sometimes better portrayed in oblique or lateral views.

Not infrequently, a subdiaphragmatic abscess may reveal a horizontal fluid level above which a pocket of gas is present, conforming with the dome of the diaphragm or taking the shape of the upper segment of a circle (fig. 3). This type of infection is caused by an anaerobic or gas-producing organism. The fluid level of the abscess is visualized roentgenologically in erect and lateral decubitus views and is obliterated in views taken with the patient in the prone position. The splash or succussion sound of the fluid and air in the abscess cavity can be elicited roentgenoscopically by shaking the patient. Similar roentgenologic observations prevail in cases of an abscess of the liver which contains gas and pus (fig. 4).

sided position of the heart and by observing the passage of an opaque meal through the transposed stomach.

From the clinical aspect, probably the most important cause for the presence of gas beneath the diaphragm is a perforated viscus. Gas escaping from a ruptured peptic ulcer collects in the subdiaphragmatic space when the patient assumes the upright position and is easily recognized on the films (fig. 5). The air disappears from the subphrenic area in the roentgenogram taken with the patient in the prone position. These well known observations have been considered indisputable. Wessler and Jaches<sup>1</sup> described these findings as "such a characteristic feature of the roentgen plate that it may be regarded as positive evidence of free air

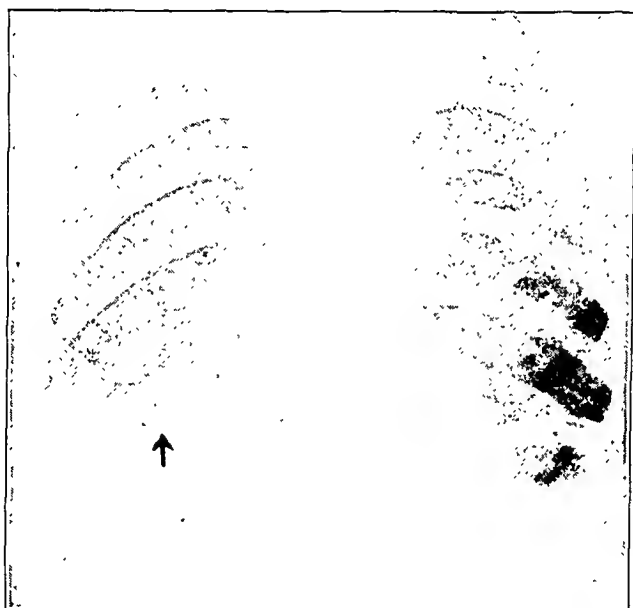


Fig. 5.—A collection of gas under the diaphragm in a patient with perforation of a duodenal ulcer.

or other gas in the peritoneal cavity." Nevertheless, there is another condition which may be readily confused with such a collection of gas and which must be borne in mind in order to avoid serious error.

In the normal person, the hepatic flexure of the colon is found immediately beneath the lower border of the liver. On rare occasions, however, this part of the colon may be found to lie between the diaphragm and the right lobe of the liver. Whether the malposition is congenital or acquired, it is usually observed on flat roentgenograms of the abdomen because of the presence of gas in the interposed segment

1. Wessler, H., and Jaches, L.: *Clinical Roentgenology of Diseases of the Chest*, Troy, N. Y., The Southworth Company, 1923, p. 509.

prone position? What was the significance of the thin, dense bands traversing the collection of air? The opinion was expressed that the shadow between the diaphragm and the liver represented not free gas but an interposition of a gas-filled hepatic colon. The traversing thin bands were probably caused by the haustrations of the interposed bowel. The unchanged appearance of the gas shadow in views taken with the patient in both positions, erect and prone, indicated that there was a hepatodiaphragmatic interposition of the hepatic flexure. That free

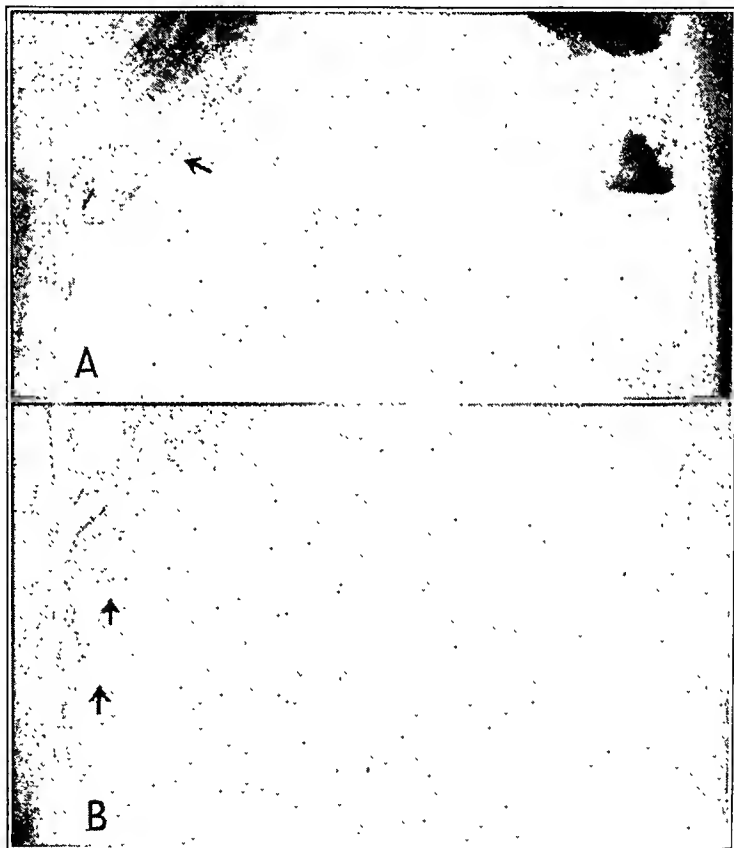


Fig. 6.—*A*, a large collection of subdiaphragmatic gas in a patient with a perforated prepyloric ulcer. Observe the fluid level on the right and the opaque band traversing the air collection (arrow). The roentgenogram was taken with the patient in the erect position. *B*, view of the chest of the same patient in the prone position. A considerable amount of gas is still present between the diaphragm and the liver. The fluid level has disappeared and several thin bands (arrows) are observed. The gas shadow represents a hepatodiaphragmatic interposition of the hepatic flexure, and the traversing bands indicate the haustral shadows. The films show the probable presence of free gas, as evidenced by the fluid level in the erect views in addition to the interposition of the gas-filled colon.

observations were highly suggestive of an advanced gastric malignant process extending to and encroaching on the esophagus.

In successive studies over a period of several weeks, the interposition of the hepatic flexure was not a constant observation. Although this interposition was present on most of the roentgenograms, on several of them the bowel was not shown to be interposed but remained abnormally high. These roentgen observations were clearly visualized with a barium sulfate meal. The right diaphragmatic cusp occupied a normal position and showed free respiratory excursions. Insufflation of the bowel with air (Bastedo), although not entirely satisfactory because of the patient's general weakness and his inability to cooperate, demonstrated an unusually high position of the hepatic flexure (fig. 8).

*Comment.*—In this case a chronically ill patient presented the clinical and roentgenologic evidence of a carcinoma of the cardia. An inci-

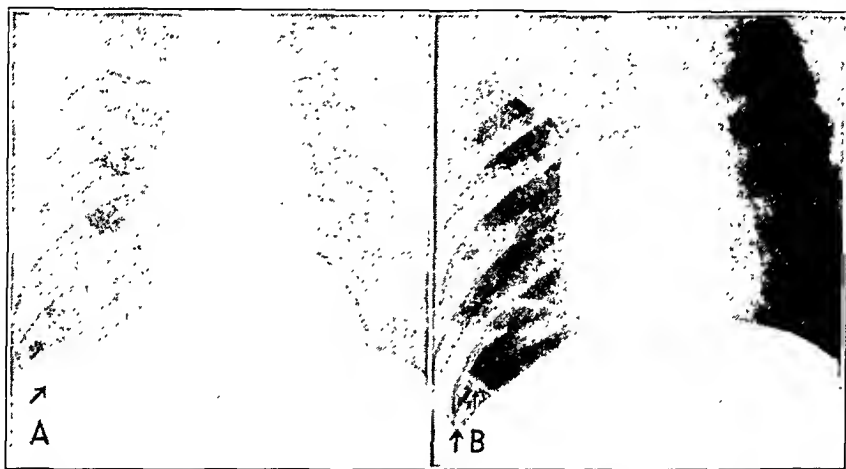


Fig. 7.—*A*, posteroanterior roentgenogram with the patient in the erect posture, showing a trace of gas in the right subphrenic space. Observe the faint shadow of a traversing haustral band (arrow). The view shows an interposition of the hepatic flexure between the liver and the diaphragm. *B*, view of the chest of the same patient in the oblique position. The gas-filled hepatic flexure and its haustral bands (arrows) are best seen in this view.

dental but inconstant observation was the high position of the gas-filled hepatic flexure, which frequently was demonstrated to be interposed between the diaphragm and the liver.

Both case reports present instances of hepatodiaphragmatic interposition of the hepatic flexure. In the first case the interposition tended to obscure the positive roentgenologic evidence necessary to establish the diagnosis of a ruptured viscus, and in the second the anomalous position of the hepatic flexure colon was apparently of no clinical importance. In both cases the roentgen findings were alike, namely, the presence of gas between the diaphragm and the liver, which sometimes

The exact causative factors in interposition are unknown. Usually, patients presenting its symptoms show an anomaly in the length of the transverse colon, which is the cause enabling the hepatic flexures to reach such a high position. Other factors are distention of the colon, with rotation on its mesentery, resulting in its elevated position in the abdomen (Viator<sup>7</sup>), hepatoptosis, with or without shrinkage in the size of the liver and loss of its plasticity (Wessler and Jaches,<sup>1</sup> Assmann,<sup>8</sup> Dehn,<sup>9</sup> and Zucchi<sup>10</sup>), an anomalous development or weakness in the hepatic ligaments (Podkaminsky<sup>11</sup>) and varying degrees of weakness or malfunction of the diaphragm (Slavin<sup>12</sup>). Probably any one of these causative factors or a combination of several may operate in the production of interposition of the rising meteoric colon. When the close contact between the liver and the diaphragm is weakened by any of the causes just mentioned, whether it be paresis of the diaphragmatic cusp due to phrenicectomy on the right side, or ptosis and rotation of the liver as a result of its shrinkage or of defects in its ligamentous attachments, there is a predisposition to hepatodiaphragmatic interposition, provided the length of the colon is sufficient to enable it to rise to this unusual position.

Uspensky,<sup>5</sup> however, stated that as a result of inflammation in the region of the colon adhesions form which fix the bowel in a bizarre position. Soupault,<sup>13</sup> Trémolières and Pierron,<sup>14</sup> Trémolières and Tardieu,<sup>15</sup> Bürger<sup>16</sup> and Weiland<sup>17</sup> emphasized the possibility that some

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# MECHANICS OF SIMPLE INTESTINAL OBSTRUCTION

## AN EXPERIMENTAL STUDY

LOUIS SPERLING, M.D.

MINNEAPOLIS

An enormous amount of research has yielded considerable information about intestinal obstruction and has resulted in the modification of previous concepts. Admitting that progress has been made, it is evident from a perusal of recent figures on mortality that much remains to be learned. Christopher,<sup>1</sup> Miller<sup>2</sup> and others have recently reported mortality rates varying between 40 and 60 per cent. When a disease carries such a mortality, no apology need be made for presenting further experimental studies. The fact that over 5,000 articles dealing with intestinal obstruction are on file in the library of the Surgeon General is an indication of the interest of physicians in this disease and an admission that their knowledge of the subject is far from complete.

It is evident that when complete knowledge of the physiologic changes that occur in intestinal obstruction is acquired, physicians will be better equipped to cope with the problem. Any alteration of normal physiology which takes place must be secondary to the stasis which is the immediate effect of intestinal obstruction. Stasis leads to distention and to an increase of intraenteric pressure, and these are the primary causes of the complications which appear when obstruction occurs. The effect of distention on the wall of the bowel is best stated in terms of the effect of various degrees of increased intraluminary pressure. This work deals with the subject of increased intraenteric pressure as it occurs in simple ileal obstruction and the effects of such pressure on the structure, the function and the permeability of the intestinal wall.

This presentation is concerned only with a study of the mechanism of simple obstruction of the ileum. The problem of strangulation obstruction is not of concern here, except as features of strangulation may attend increased intraenteric pressure. A consideration of the

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Abridgment of thesis submitted to the Faculty of the Graduate School, University of Minnesota, in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Surgery.

1. Christopher, F., and Jennings, W. K.: Mortality in Intestinal Obstruction, *Ann. Surg.* 99:332-337, 1934.

2. Miller, C. J.: A Study of Three Hundred and Forty-Three Surgical Cases of Intestinal Obstruction, *Ann. Surg.* 89:91-107, 1929.

reached 20 cm. of water. On one occasion, after the intake of food, a pressure of 35 cm. of water was noted.

The intraenteric pressure was determined in 25 dogs with low ileal obstruction of one to seven days' duration.<sup>7</sup> The pressure ranged from 4 to 19 cm. of water, or roughly four times the normal pressure. Active peristalsis was uniformly present even after seven days of obstruction (fig. 1). The intraenteric pressure in this series apparently increased with the duration of the obstruction. It was observed that the sustained pressure in low ileal obstruction was seldom above 14 cm. of water (table 1). These data are in accord with the findings of Owings and his associates.<sup>3</sup>

Opportunity has also been afforded to determine the intraenteric pressures at the time of the operation in 6 clinical cases of mechanical

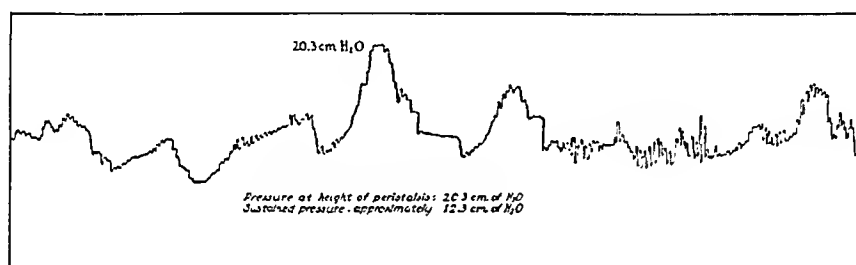


Fig. 1.—Intraenteric pressure and peristalsis in simple ileal obstruction of seven days' duration. (Pressure at height of peristalsis, 20.3 cm. of water; sustained pressure, approximately 12.3 cm. of water.)

TABLE 1.—Sustained Intraenteric Pressure in Dogs with Simple Ileal Obstruction

Dog	Duration of Obstruction, Days	Pressure, Cm. H <sub>2</sub> O	Dog	Duration of Obstruction, Days	Pressure, Cm. H <sub>2</sub> O
1	1	8	11	4	14
2	2	4	12	4	10
3	2	6	13	4	7
4	2	12	14	4	12
5	2	6	15	4	10
6	3	10	16	4	8
7	3	12	17	4	10
8	4	8	18	7	19
9	4	10	19	7	12
10	4	14			

obstruction of the small bowel.<sup>8</sup> The sustained pressure varied between 4 and 18 cm. of water. With peristaltic activity, pressures rose to 20 and then to 30 cm. of water.

7. Sperling, L.; Paine, J. R., and Wangenstein, O. H.: Intra-Enteric Pressure in Experimental and Clinical Intestinal Obstruction, *Proc. Soc. Exper. Biol. & Med.* **32**:1504-1506, 1935.

8. Sperling, L.: Role of the Ileo-Cecal Sphincter in Cases of Obstruction of the Large Bowel, *Arch. Surg.* **32**:22-49 (Jan.) 1936.



there was a definite shortening of the intestine (Sperling and Wangenstein<sup>12</sup>). The length of a segment which before obstruction measured 12 inches (30 cm.) decreased by as much as one third after obstruction. Statistically, it was shown that the intestine is shortened to a significant degree in simple ileal obstruction. Hypertonicity of the obstructed intestine, with marked contraction of the longitudinal muscles, is probably responsible for this shortening. The shortening is sufficient to account for some of the increased weight of the wall of the bowel which is observed in simple ileal obstruction.

TABLE 2.—*Shortening of the Bowel in Simple Ileal Obstruction—Ultimate Length of Consecutive 12 Inch Segments from Site of Obstruction, Ileum to Jejunum*

Dog	Duration of Obstruction, Days	Segments								
		1	2	3	4	5	6	7	8	9
1	4	8.75	9.00	7.50	9.00	....	....	....	....	9.50
2	4	12.00	12.00	8.50	9.50	9.50	....	....	....	9.50
3	4	9.50	9.00	8.00	7.00	....	....	....	....	....
4	4	8.25	7.00	7.25	7.25	....	....	....	....	7.75
5	4	7.25	6.75	7.00	7.00	8.25	8.50	....	....	8.25
6	4	9.25	8.75	8.50	13.50	6.75	....	....	....	7.25
7	2	9.50	10.00	10.00	11.50	10.50	12.00	11.00	....	9.00
8	2	8.75	8.25	7.75	8.75	7.75	8.50	9.25	11.00	10.00
9	1	10.50	10.50	(Only two lower segments marked off)						
10	1	8.50	5.50	(Only two lower segments marked off)						
11	3	10.00	8.00	(Only two lower segments marked off)						
12	3	8.50	9.75	(Only two lower segments marked off)						
Average shortening: $-2.77 \pm 0.35$ inches; $-3.47 \pm 0.40$ inches										

TABLE 3.—*Length of Consecutive 12 Inch Segments of the Small Intestine of Normal Dogs Measured After Forty-Eight Hours (Ileum to Jejunum)*

Dog 1.....	12.00	11.25	12.5	13.00	9.5	12.00	12.50	13.5	13.00	11.00	
Dog 2.....	11.25	13.25	11.0	11.25	11.0	10.25	10.25	12.0	10.75	10.25	11.0
Average decrease in length of $0.63 \pm 0.23$ inch											

#### INFLUENCE OF OBSTRUCTION ON THE WEIGHT OF THE INTESTINAL WALL AND ON ITS CONTENT OF WATER AND HEMOGLOBIN

As far as can be determined, there has been no previous estimation of changes in the weight of the intestine in simple intestinal obstruction. Opportunity to make such observations was afforded in the course of other experiments on dogs with simple obstruction of the ileum.

12. Sperling, L., and Wangenstein, O. H.: Influence of Obstruction of the Bowel upon Its Length and Weight, *Proc. Soc. Exper. Biol. & Med.* **32**:1219-1224, 1935.

decrease in weight in a retrograde manner from the obstructed ileum to the duodenum. This is due to the fact that the segments of bowel immediately above the obstruction increase most in weight while those segments of the jejunum remote from the site of obstruction increase only slightly in weight.

The results indicated in table 8 represent the relative increase in hemoglobin content of the obstructed bowel as compared with that of the

TABLE 6.—*Weight Changes of the Bowel in Simple Ileal Obstruction (1 Foot Segments Marked Off at the Time Obstruction Was Made)*

Dog	Weight, Kg.	Duration of Obstruction, Days	Weight of Consecutive 1 Foot Segments of Bowel, Jejunum to Ileum, Gm.	
1	14	4	40—32—31—26—29—32—41	
2	13	4	21—22—23—30—34	
3	14	4	41—45—44—42—57—58	
4	18	4	27—25—33—33—37—35	
5	8	4	23—16—18—19—35	
6	17	4	31—31—35—50	
7	10	4	24—20—21—21—27—27—27—39	
8	11	2	22—22—20—19—22—23—22—26	
9	13	2	25—24—22—23—23—23—24—26—30	
10	14	3	21—20—22—22—29—37	
Average weight	13		Average weight of terminal portion of ileum per foot.....38.5 Gm. Percentage of increase.....34	

TABLE 7.—*Water Content of Normal Bowel as Compared with Obstructed Bowel*

Normal Bowel			Obstructed Bowel		
Dog	Jejunum- %	Ileum, %	Dog	Jejunum, %	Ileum, %
1.....	76.5	72.6	1.....	82.4	85.1
2.....	79.6	78.1	2.....	84.7	85.0
3.....	76.3	78.2	3.....	84.1	80.5
4.....	77.2	77.2	4.....	78.0	80.9
5.....	78.1	77.7	5.....	77.4	83.3
6.....	76.2	75.5	6.....	83.3	83.4
7.....	75.9	77.8	7.....	81.2	81.2
8.....	70.2	72.7	8.....	81.0	78.4
9.....	77.4	77.5	9.....	80.4	83.5
Average.....	76.3	76.5	Average.....	81.0	83.5
Mean difference	±1.7	±1.73	Mean difference	±2.39	±2.02

In simple ileal obstruction there is approximately 4.7 per cent increase of the water content of the jejunum and 7 per cent increase of the water content of the ileum.

normal bowel (experiment performed on the same dog prior to obstruction). There is a wide range of individual variation. It is noteworthy that an increase of more than 100 per cent is the rule. A previous study made in this laboratory by Carlson and Wangensteen<sup>13</sup> indicated that the accumulation of blood in the bowel in simple obstruction is due to stasis in the vessels and not to interstitial hemorrhage.

13. Carlson, H. A., and Wangensteen, O. H.: Histologic Study of the Intestine in Simple Obstruction, *Proc. Soc. Exper. Biol. & Med.* 29:421-424, 1932.

The tensile strength of the jejunum approached the normal, whereas that of the obstructed segment of bowel (ileum) was far below normal. In the obstructed specimens (ileum) the serosa usually split at the antimesenteric border at a pressure of about 100 to 300 mm. of mercury and soon burst, whereas in the specimens of normal ileum the serosa was usually able to resist a pressure of more than 400 mm. of mercury.

TABLE 9.—*Tensile Strength (Bursting Pressure) of Normal Bowel\**

Dog	Pressure (Mm. Hg) at Which Serosa Split		Pressure (Mm. Hg) at Which Bowel Burst	
	Ileum	Jejunum	Ileum	Jejunum
1.....	360 a	210 a	620	400
2.....	300 a	660 a	560	660
3.....	540	400 p	540	400
4.....	480 a	440	480	440
5.....	660 a	600 a	Ends blew out	
6.....	540 a	610 a	Ends blew out	
7.....	700 a	540 a	700	540
8.....	1,060 a	820 a	1,060	820
9.....	560 p	640 p	560	640
10.....	700 p	780 a	700	780
11.....	300 m	220 m	660 m	500 a
12.....	1,080 m	400 a	1,080	820
Mean.....	606.7	526.7	696	600

\* In this table a indicates antimesenteric border; p, paramesenteric border, and m, mesenteric border.

TABLE 10.—*Tensile Strength (Bursting Pressure) of Obstructed Bowel\**

Dog	Duration of Obstruction, Days	Pressure (Mm. Hg) at Which Serosa Split		Pressure (Mm. Hg) at Which Bowel Burst	
		Ileum	Jejunum	Ileum	Jejunum
1.....	6	195 a	...	200-End b. o.	
2.....	6	220 a	240	230	540
3.....	7	200	200	250	225
4.....	7	90 a	190 a	180 a	260 a
5.....	7	200	200	200	200
6.....	7	200 a	500 a	280	760
7.....	5	210 a	420 a	250 m	620 m
8.....	5	360 a	560 p	480 m	560 p
9.....	5	260 a	360 a	360 a	400 a
10.....	6	400 m	500	460 m	520 a
Mean.....		233.51	352.2	292.0	453.9

\* In this table a indicates antimesenteric border; p, paramesenteric border, and m, mesenteric border.

These observations appear to justify the following conclusions:

1. The intestinal wall in simple obstruction cannot withstand as high an intraenteric pressure as can the wall of the normal bowel.

2. The portion of the bowel just above the site of obstruction is most affected.

3. The most frequent site of tearing of the serosa and of rupture is the antimesenteric border of the bowel.

was absent at pressures below 10 mm. of mercury. It usually began at pressures varying between 10 and 15 mm., the critical pressure for that segment of bowel (fig. 2).

With increasing distention the peristaltic waves were usually augmented in size until a pressure varying between 15 and 30 mm. of mercury was reached.

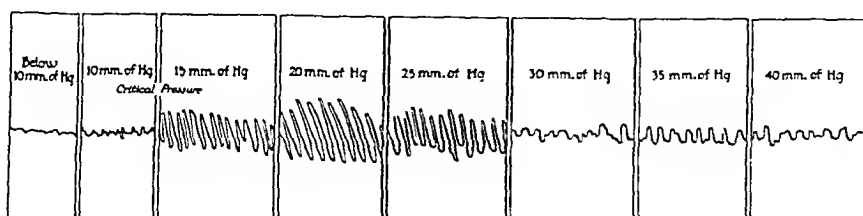


Fig. 2.—Effect of increased intraenteric pressure on peristalsis of the ileum.

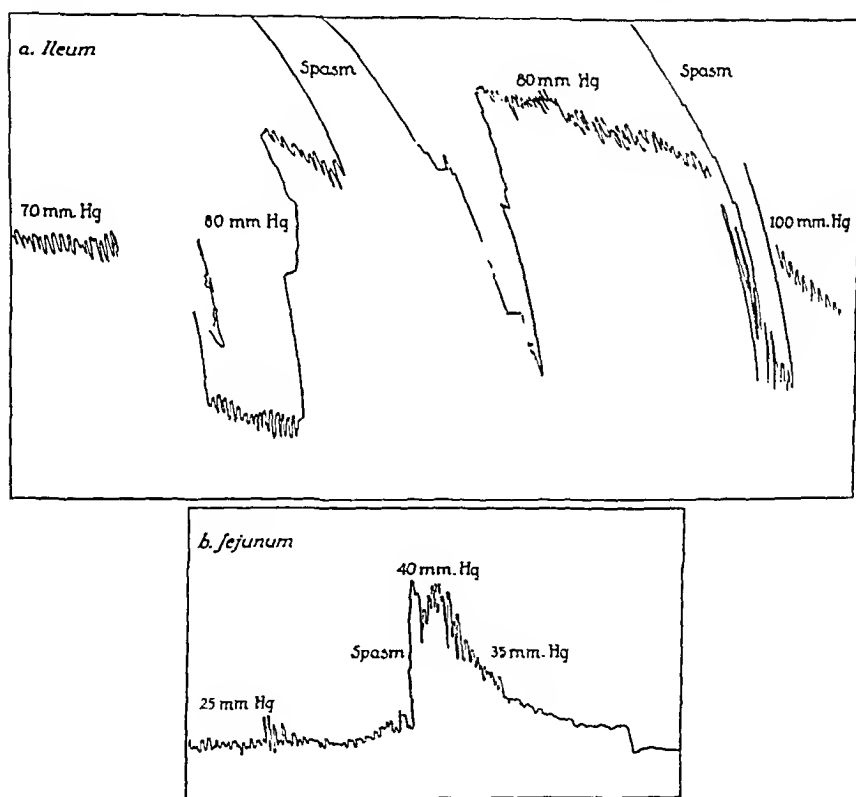


Fig. 3.—Spasm induced by increased intraenteric pressure.

After a pressure of 30 mm. of mercury was reached there was no further increase in the size of the peristaltic waves.

When intestinal loops were subjected to pressures varying between 40 and 80 mm. of mercury for sixty minutes or more, spasmodic contractions of the bowel similar to those occurring in the clinical subjects, that is, to intermittent colic, were occasionally seen (fig. 3). This, however, was not a constant finding. With the animal under light anesthesia, these contractions were accompanied by evidence of pain.

degree on the response of the intestinal musculature to the distention incident to stasis than on simple increase of content. It was noted that at a pressure of 25 mm. of mercury, with active peristalsis in the jejunum, aspiration of 10 cc. from the ileal loop had no effect on the pressure. Apparently changes in tone make up for small changes in volume. This conforms with the law of postural tone as postulated by Sherrington. Massive reduction of volume, that is, sudden decompression, results, however, in a lowering of the pressure. This is accompanied by a great increase in tone, as evidenced by the violent peristalsis and the consequent rapid increase of intraluminary pressure when distended loops of bowel are rapidly decompressed.

No doubt some degree of protection is afforded the wall of the bowel by its ability to dilate and to accommodate itself to increased tension. There is a progressive increase in its diameter in proportion to the duration of the obstruction; that is, the diameter of bowel obstructed for a period of ninety-six hours is greater than that of bowel obstructed for only twenty-four hours. This increase is due in part to stretching caused by the increased intraenteric pressure, but it is principally due to relaxation of the intestinal musculature. The tension on any part of the intestine is dependent on its circumference and on the intraenteric pressure. It is well known that after complete obstruction of the left half of the colon perforation of the bowel is observed most frequently in the cecum. This may be due to the fact that, having the greatest lumen, it is subjected to the greatest pressure.

Sustained high pressure is more damaging to the bowel than intermittent pressure, even if the latter is of so high a degree as to cause local blanching. Ample opportunity is afforded the bowel to dilate and to return to its normal state in the interval between contractions. This pressure-free interval is lacking, of course, when the intraenteric pressure is sustained at a constant level. The insignificant histologic changes observed in experimental and clinical cases of simple intestinal obstruction may be accounted for by this ability of the bowel to relax and so accommodate itself to elevated tension. This phenomenon of relaxation undoubtedly also occurs to some degree in closed intestinal loops, but it is evident that sooner or later the elevated pressure must become constant, bringing with it the danger of strangulation.

#### EFFECT OF DISTENTION ON INTESTINAL SECRETION

Enderlen and Hotz<sup>19</sup> in 1911 noted that in the later stages of obstruction there was extravasation of fluid into the bowel. More

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19. Enderlen, E., and Hotz, G.: Ueber die Resorption bei Ileus und Peritonitis, Mitt. a. d. Grenzgeb. d. Med. u. Chir. 23:755, 1911.

of the ileum. In low ileal obstruction, especially in obstruction of the closed loop type which occurs in the colon because of the competent ileocecal sphincter, the bowel cannot decompress itself by reversed peristalsis and regurgitation; thus, the increased secretion results in progressive augmentation of the distention.

Under the influence of obstruction, the total amount of fluid in the lumen of the bowel is increased by the response of the intestine to distention. Since the intestine fails to reabsorb this fluid, the cause of dehydration is apparent.

#### INFLUENCE OF OBSTRUCTION AND INCREASED INTRAENTERIC PRESSURE ON INTESTINAL ABSORPTION

It is generally conceded that the contents of both the obstructed and the normal bowel are toxic if injected intravenously. The manner and the routes of toxic absorption from the obstructed bowel are still subjects of considerable speculation and debate. The possible avenues by which toxic material of any kind may be absorbed are (1) the mesenteric veins, (2) the lymphatics and (3) the intestinal wall (transperitoneally by diffusion).

*Venous Absorption.*—Decreased absorption through the mesenteric veins of such substances as dextrose, salt, iodide, strychnine and histamine has been observed by many investigators. It is remotely possible, however, that the factor of selective absorption may play a role in determining the degree of absorption through the veins in simple intestinal obstruction. It may be that the bowel in a condition of obstruction becomes permeable to a toxin which is different from any of the substances used in experiments on animals.

This decrease of absorption, both quantitative and qualitative, has been attributed to the increase of intraenteric pressure which occurs in intestinal obstruction. Gatch and Culbertson<sup>22</sup> have investigated the absorption of specific substances, such as bromides and alcohol, from the normal bowel under moderately increased intraenteric pressure. They found that for pressures between 10 mm. of mercury and the diastolic blood pressure of the animals used in the experiments the rate of absorption of these substances is relatively constant.

The deleterious effect of simple ileal obstruction on the absorption of water from loops of ileum is illustrated by the fact that under identical experimental conditions closed loops of normal ileum absorbed approximately 90 per cent of the amount of water necessary to fill them, while loops of ileum which had been subjected to previous obstruction were able to absorb less than 10 per cent (table 11).

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22. Gatch, W. D., and Culbertson, C. G.: Circulatory Disturbances Caused by Intestinal Obstruction, *Ann. Surg.* 102:619-635, 1935.

This amount of pressure (40 cm.) is of course the optimal level for the absorption of water only for the particular segment of the bowel investigated (the lower part of the ileum). From the work of

TABLE 12.—*Effect of Increased Intraenteric Pressure on Absorption of Water from Loops of Normal Ileum*

	Dog	Weight, Kg.	Amount Absorbed, Cc.	Ratio, Cc. per Kg. per Hour
10 cm. water	1.....	15.0	100	6.6
	2.....	22.7	105	4.6
	3.....	26.4	165	6.2
	4.....	26.4	125	4.7
	5.....	12.3	70	5.7
	6.....	15.0	95	6.3
	7.....	19.5	115	5.9
	8.....	16.8	70	4.2
Average ratio at 10 cm.....				5.5
20 cm. water	9.....	20.4	236	11.5
	10.....	20.9	190	9.1
	11.....	14.1	150	12.7
	12.....	13.2	120	9.1
	13.....	15.4	180	8.8
	14.....	9.1	125	13.7
	15.....	7.3	60	8.2
	16.....	12.7	160	12.6
Average ratio at 20 cm.....				10.5
40 cm. water	18.....	19.1	285	14.9
	19.....	14.1	170	12.1
	20.....	10.0	150	15.0
	21.....	12.4	130	10.5
	22.....	17.7	190	10.7
	23.....	9.1	110	12.1
	24.....	8.6	115	13.4
Average ratio at 40 cm.....				12.7
60 cm. water	25.....	20.5	210	10.2
	26.....	17.3	125	7.2
	27.....	12.7	160	12.6
	28.....	20.5	150	7.3
	29.....	10.0	95	9.5
	30.....	12.3	120	9.7
Average ratio at 60 cm.....				9.4
80 cm. water	31.....	6.8	55	8.1
	32.....	9.5	50	5.3
	33.....	9.5	70	7.4
	34.....	15.0	50	3.3
	35.....	18.2	120	6.6
Average ratio at 80 cm.....				6.1
100 cm. water	36.....	11.4	55	4.8
	37.....	12.3	35	2.8
	38.....	14.5	72	4.9
	39.....	17.3	105	6.0
	40.....	11.8	75	6.3
Average ratio at 100 cm.....				4.9

Dragstedt,<sup>24</sup> it may be surmised that the optimal level is lower in the jejunum and higher in the proximal portion of the colon, as he has

24. Dragstedt, C. A.; Lang, V. F., and Millet, R. F.: Relative Effects of Distention on Different Portions of the Intestine, *Arch. Surg.* 18:2257-2263 (June) 1929.

on intestinal absorption. Leubuscher ascribed the primary increase of absorption to unfolding of the mucosa and the secondary decrease to interference with the blood supply. Wells<sup>27</sup> found that the absorption of saline solution from closed loops was in direct proportion to the intraenteric pressure. However, his studies include pressures only up to 16 cm. of water. Elman and Aird,<sup>6</sup> in two experiments on animals and in one observation on a human being, showed essentially the same result which was obtained in these experiments. They noted maximum absorption at 50 cm. of water. At higher pressures (85 to 90 cm. of water), absorption did not take place. In their single experiment on a human being, the maximum absorption occurred at a pressure of

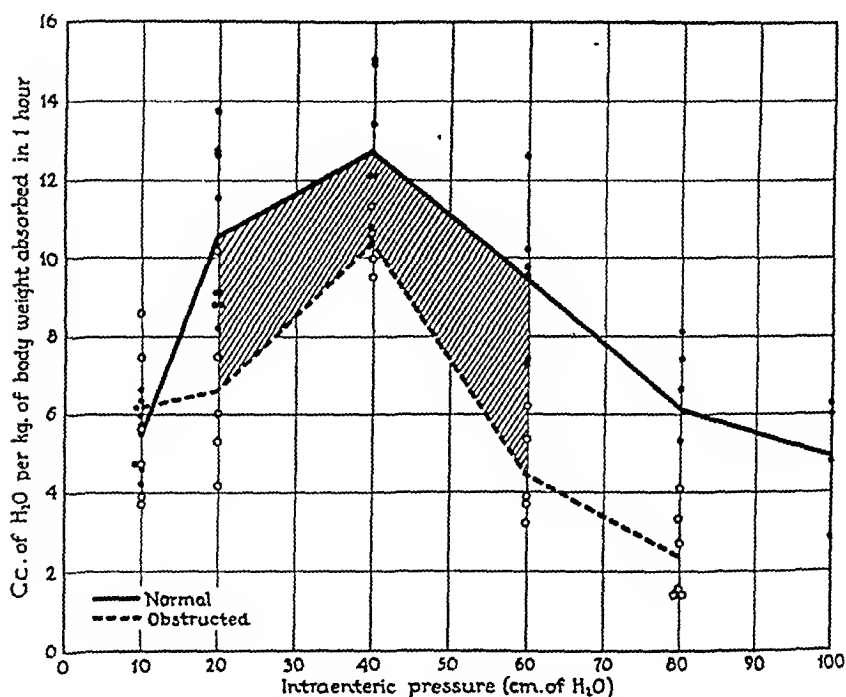


Fig. 5.—Effect of increased intraenteric pressure on the absorption of water from the normal and from the obstructed ileum. The shaded areas indicate significant difference between means.

40 cm. of water and fell progressively on increase of pressure until at a pressure of 70 cm. of water definite secretion into the loop occurred.

Absorption of Strychnine from the Normal and From the Obstructed Ileum: Though the avenues by which absorption may occur in obstruction are known, it is extremely difficult to ascertain definitely through

27. Wells, H. S.: Passage of Materials Through Intestinal Wall: Relation Between Intra-Intestinal Pressure and the Rate of Absorption of Water, *Am. J. Physiol.* 99:209-220, 1931.



The obstructed bowel absorbs only a fraction of the amount of water taken up by a similar segment of normal intestine under identical experimental conditions. Increase of the intraintestinal pressure results in a progressive increase in the absorption of water from the normal bowel until a pressure of 40 cm. of water is reached. Higher pressures produce a fall of the rate of absorption to below the normal rate. The same holds true, but to a lesser degree, in the obstructed bowel. Pressures above 75 mm. of mercury effectively prevent venous absorption.

*Lymphatic Absorption.*—An attempt was made to determine the occurrence of lymphatic absorption in simple intestinal obstruction and with increased intraenteric pressures.<sup>29</sup>

*Absorption of Dyes Via the Lymphatics in Simple Ileal Obstruction:* Fifteen normal cats were given trypan blue by stomach tube and 5 by enteral injections. In none was the dye visible in the regional lymph nodes at intervals of two to forty-eight hours. When cats with simple ileal obstruction were given the dye by stomach tube none appeared in the lymphatics. When this dye was injected into the bowel at the time the obstruction was produced, 3 of 8 cats showed colored nodes. When intestinal stasis was induced by chemical peritonitis (with iodine) 1 of 5 cats showed blue lymph nodes.

*Absorption of Dyes from the Lumen of the Intestine Under Increased Intraenteric Pressure:* Closed ileal loops were prepared in 12 cats and the loops distended with dye until the walls became tense (marked increase of intraenteric pressure). Ten of the 12 cats at autopsy (twenty-four to seventy-two hours) showed blue nodes. In several of these experiments the dye, as it was injected into the lumen of the bowel under pressure, could be seen to enter Peyer's patches after five or ten minutes and subsequently to enter the lymph vessels of the mesentery. This procedure was repeated in vitro with fresh excised viable segments of normal and obstructed bowel of the cat, with the following results: Pressures of 100 mm. of mercury in a normal loop forced the dye out into the lymphatics in five minutes. In another normal loop a pressure of 50 mm. of mercury forced the dye into the lymph vessels in one hour. When a fresh viable loop excised from a cat with simple ileal obstruction of forty-eight hours' duration was subjected to a pressure of 40 mm. of mercury, dye appeared in the lymph vessels in thirty minutes. When nonviable loops were subjected to increased intraenteric pressure, the dye, in addition to being forced rapidly into the lymphatics, permeated the wall of the intestine directly (table 15).

*Absorption of Bacteria Via the Lymphatics:* The absorption of bacteria through the lymphatics was studied in the following manner: A heavy suspension of *Bacillus pyocyaneus* was injected into the ileums of 6 normal cats. Preliminary cultures of regional lymph nodes were sterile. Cultures of material taken from the nodes one hour after the intraenteric injection showed *B. pyocyaneus* in 2 cases and failed to do so in 4; in 2 of the latter, cultures of *B. pyocyaneus* were obtained when the cats were again operated on after twenty-four hours. In 2 additional cats in which the bacterial suspension was introduced into closed loops

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29. Sperling, L., and Wangenstein, O. H.: Lymphatic Absorption in Simple Obstruction: Significance of Distention upon Its Occurrence, *Proc. Soc. Exper. Biol. & Med.* **33**:22-26, 1935.

high correlation exists between the increased intraenteric pressure in obstruction and the degree of lymphatic absorption.

It appears that the regional lymph nodes normally serve as an effective barrier against the overwhelming absorption of bacteria into the blood stream via the mesenteric lymphatic channels. True bacteremia probably does not occur and is probably not the cause of death in uncomplicated intestinal obstruction, as cultures producing the test organism could not be obtained in material taken from the thoracic duct. The lymph nodes yielding the organisms acted as efficient barriers and prevented centripetal invasion. Toxemia of bacterial origin or from lymphatic absorption of toxic amines from the bowel, however, has not been wholly excluded.

**Significance of Lymphatic Absorption in Simple Intestinal Obstruction:** An attempt was made to evaluate the significance of lymphatic absorption in the lethal issue of simple intestinal obstruction by interruption of the lymphatic channels. This was accomplished by ligating and cutting the lymphatic pedicle of the mesenteries in 4 cats after the establishment of simple ileal obstruction. The period of survival was not greater than that of the control animals, in which the lymphatic pedicle was not severed.

These observations seem to justify the conclusion that intestinal obstruction and increased intraenteric pressure increased the absorption of dyes and of bacteria into the regional lymph nodes. No evidence was, however, adduced to indicate that this occurrence is of great significance in the lethal issue of simple intestinal obstruction in animals.

*Transperitoneal Absorption.*—The wall of the normal viable bowel is resistant to the passage of toxic material from its lumen into the peritoneal cavity. Most investigators are agreed that transperitoneal passage of any material does not take place unless extreme increases of intraintestinal pressure obtain or unless gross injury to the bowel wall is present. Schönbauer,<sup>31</sup> Gatch,<sup>28</sup> Chenuth,<sup>32</sup> and others have advanced the hypothesis that death following intestinal obstruction is due to the absorption of toxins which have passed through the wall of the bowel into the peritoneal cavity.

Stone and Firor,<sup>5</sup> Gatch,<sup>28</sup> Dobyns and Dragstedt<sup>33</sup> and others have indicated that increased intraenteric pressure may force toxic materials through the intestinal wall. Gatch's work on the permeability of the bowel to hydrocyanic acid under increased tension was repeated

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31. Schönbauer, L.: Die Fermente in ihrer Beziehung zu gewissen Erkrankungen der Gallenblase und zum Ileus, *Arch. f. klin. Chir.* **130**:427-462, 1924.

32. Chenuth, A.: L'experimentation dans l'occlusion mecanique du jejunum-ileum, *Rev. de chir., Paris* **64**:474-834, 1926.

33. Dobyns, G. J., and Dragstedt, C. A.: Intra-Intestinal Pressure and Absorption from the Intestine, *Proc. Soc. Exper. Biol. & Med.* **30**:707-709, 1933.

at respective pressures of 40 and 130 mm. of mercury. The dye had not permeated the bowel after one hour of distention. However, when ileal loops from 2 cats with intestinal obstruction, dead six and eight hours respectively, were subjected to distention at a pressure of 100 mm. of mercury, the nonviable bowel permitted the dye to pass directly through its wall in fifteen to thirty minutes. When a 1 per cent solution of gentian violet was injected into the intestinal lumen in cats with simple obstruction and obstruction of the closed loop type, only a slight staining of the mucosa was present in a few instances on microscopic section of the bowel (Churchman's method<sup>35</sup>). As this was not a constant finding and was present only in cats dead several hours, it was assumed that the penetration of the mucosa was a postmortem phenomenon. In none of the cats could transperitoneal passage of the dye be demonstrated by wrapping gauze about the outside of the bowel. In 1 experiment the dye was introduced into the loop under high pressure so that the loop was very tense. When the cat was killed seventy-two hours later (moribund), several purple spots were visible on the antimesenteric border. These were judged to be nonviable necrotic areas through which the dye had passed.

**Correlation of the Viability of the Intestinal Wall with Its Permeability in Simple Ileal Obstruction:** The following experiments were undertaken to determine whether any correlation exists between the permeability and the viability of the bowel in simple ileal obstruction.

Fifteen cats with simple ileal obstruction of six to one hundred and sixty-eight hours' duration were killed at definite intervals after the obstruction, and the viability and permeability of the loops were noted in the following manner: The terminal 4 inches (10 cm.) of the obstructed bowel was removed, and the closed segment was at once immersed in a beaker of Ringer's solution (temperature 37 C.). The viability of the segment was determined by noting the length of time during which it reacted by contraction to a measured electrical stimulus repeated every fifteen minutes. The loop was considered to have lost its viability when no contraction appeared after prolonged stimulation. Permeability of the bowel was determined by immersing the segments, filled with potassium ferrocyanide, at intervals of fifteen minutes into another beaker of Ringer's solution, containing ferric chloride, and noting the time at which the characteristic prussian blue color appeared.

The segments of bowel from the cats with intestinal obstruction were all viable and showed no permeability when first removed. They remained viable for periods varying between fifteen minutes to one and one-quarter hours after the animals were killed. Most specimens resisted permeation for some time after some impairment of viability was evident. The segments from the dead cats which had been normal and from cats already dead of intestinal obstruction were of course nonviable and showed immediate permeation. Loops obstructed for ninety-six hours or longer showed signs of impairment of viability (table 16).

In a similar study, Schempp<sup>36</sup> could not find any definite relation between the duration of obstruction and the viability of the bowel.

That a real difference in permeability and viability exists between normal bowel and obstructed bowel is shown by experiments on the

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35. Churchman, J. W.: The Selective Bacteriostatic Action of Gentian Violet and Other Dyes, *J. Urol.* **11**:1-18, 1924.

36. Schempp, E.: Zur Frage der Durchlässigkeit der Darmwand für gelöste Stoff, insbesondere beim Darmverschluss, *Beitr. z. klin. Chir.* **143**:728-736, 1928.

zation of normal and previously obstructed bowel. Still, evidence of transperitoneal absorption does not ordinarily appear until there is anatomic evidence of damage to the wall of the intestine, as will be shown in some following experiments.

These observations appear to warrant the conclusion that transperitoneal absorption in simple intestinal obstruction may occur, but only through devitalized segments of bowel subjected to distention, and that the obstructed bowel under similar experimental conditions is more permeable to strychnine than is the normal bowel.

#### EFFECT OF PROLONGED DISTENTION ON THE STRUCTURE, VIABILITY AND PERMEABILITY OF THE WALL OF THE BOWEL

Any pathologic changes in the bowel as a consequence of increased intraenteric pressure must be secondary to the effect of this increased pressure on the circulation of the intestinal wall.

Kocher<sup>37</sup> was the first to recognize the significance of increased intraenteric pressure. Many American investigators have since referred to the obvious disturbance of circulation and consequent impairment of function of the intestine as a result of increased intraenteric pressure (Van Zwahlenberg,<sup>38</sup> Dragstedt,<sup>33</sup> Gatch and others).

Van Zwahlenberg<sup>39</sup> attempted to explain the pathologic changes occurring in intestinal obstruction on the basis of anoxemia of the wall of the bowel. According to his research, stasis of blood results in a decreased oxygen supply, which affords excellent opportunity for the development of infection and its sequelae, gangrene, necrosis and perforation of the intestinal wall. He cited experimental evidence presented by Burget and Visscher<sup>40</sup> to show that the bowel deprived of its blood supply uses up all available oxygen very rapidly. Bacteria, especially anaerobes and facultative anaerobes, grow well in asphyxiated tissue. There can be no doubt that partial asphyxia of the wall of the bowel, due to stasis of blood, occurs in simple intestinal obstruction.

The stagnant contents of obstructed loops form an excellent culture medium for the growth of bacteria. Thus, bacterial growth may invade the partially asphyxiated tissues of the bowel, with resulting pathologic

37. Kocher, T.: Ueber Ileus, Mitt. a. d. Grenzgeb. d. Med. u. Chir. 4:195-230, 1899.

38. Van Zwahlenberg, C.: Hydraulic Vicious Circle as It Develops in Intestine: Effect of Intra-Intestinal Pressure on the Pathology and Physiology of the Bowel, Am. J. Surg. 18:104-112, 1932.

39. Van Zwahlenberg, C.: Hydraulic Vicious Circle as It Develops in Acute Appendicitis, Am. J. Surg. 16:427-440, 1932.

40. Burget and Visscher, cited by Van Zwahlenberg, C.: Oxygen Lack in Hydraulic Vicious Circle, Am. J. Surg. 18:133, 1932.

40 cm. of water was tolerated for only seventeen hours before gangrene and necrosis ensued. At this pressure the loops were dilated and invariably showed large gangrenous areas with loss of viability and abnormal permeability. Loops of colon subjected to pressures of 30 and 50 cm. of water for twenty-four hours showed similar changes. Loss of viability was encountered only in necrotic areas. Abnormal permeability of the bowel was present through these areas, but never through viable bowel. It is significant that in 1 of these experiments the bowel did not become permeable until six hours after loss of viability was demonstrated (table 11).



Fig. 7.—Dog's ileum subjected to a pressure of 15 cm. of water for eighteen hours. Note hemorrhage into the lumen of the bowel, submucosal hemorrhage and infiltrated and necrotic areas in the muscular layers.

The microscopic observations (figs. 7, 8, 9 and 10) were as follows:

1. Congestion and dilatation of capillaries at a pressure of 10 cm. of water.
2. Extravasation of blood into the tissue spaces and into the lumen of the bowel at a pressure of 15 and 20 cm. of water.
3. Early mononuclear cellular infiltration in the submucosa, even at a pressure of 10 cm. of water.
4. Areas of gangrenous and necrotic tissue in all layers after twenty-four hours of distention at pressures of 20 or 40 cm. of water.



Fig. 9.—Dog's ileum subjected to a pressure of 40 cm. of water for twenty hours. Note hemorrhage into the lumen and necrotic areas in the submucosa and the muscular layers.

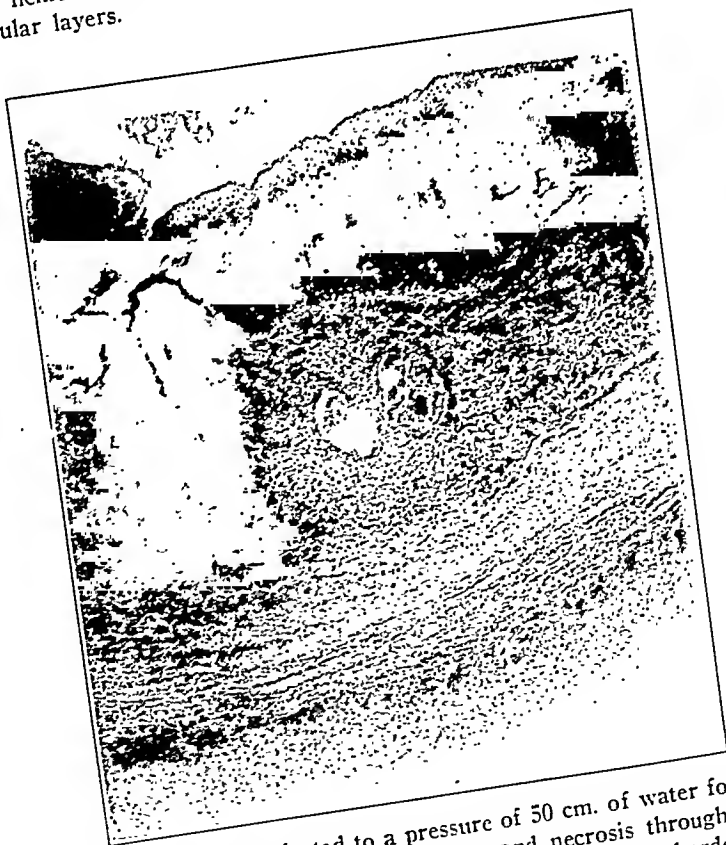


Fig. 10.—Dog's colon subjected to a pressure of 50 cm. of water for twenty-four hours. Note areas of hemorrhagic infiltration and necrosis throughout all layers of the intestinal wall. (Section taken from the antimesenteric border.)

Although many toxic substances have been isolated from the intestinal contents of animals with ileal obstruction, direct proof of their absorption and of the actual avenue of absorption is lacking. A tremendous amount of literature has accumulated dealing with the possible toxic factor, but as yet concrete evidence to the effect that a specific toxin is absorbed and is responsible for the fatal issue is not available. It is granted that the content of the obstructed bowel is toxic when injected intravenously, but so is the content of the normal bowel. The fact that such material, injected intravenously or by some other parenteral route, produces toxic symptoms does not prove anything more than that, for in carrying out such experiments the normal capacity of the mucosa to protect the organism against fatal infection and other menaces is entirely overlooked. If any toxin is absorbed through the mucosa, it may be by way of the lymphatics, since, as has been shown, absorption by all other normal avenues is decreased when the bowel is obstructed. It is significant that bacteria may be demonstrated in the mesenteric lymph nodes in far greater numbers in the obstructed bowel than in the normal bowel. Nevertheless, ligature of the lymphatic pedicle at the root of the mesentery does not prolong the survival of animals with simple intestinal obstruction.

Transperitoneal absorption must be considered a manifestation of impaired viability of the bowel which has been subjected to distention for a sufficient time to produce gross anatomic changes. Its occurrence is probably insignificant as long as the bowel remains viable, but it may become significant when a devitalized segment is subjected to prolonged distention. The intraenteric pressure, the duration of distention and the diameter of the intestinal coils determine the effect of the distention on the blood supply of the intestine and, in time, the presence or absence of gross anatomic changes and loss of viability of its wall which permit transperitoneal absorption to take place.

That the derangement of normal function which occurs at the level of obstruction is an important factor in the fatal issue is suggested by the following experiment.<sup>43</sup>

Ileosigmoidostomy was performed in 7 dogs in an attempt to alter the function of the terminal portion of the ileum by adapting it to the conditions of the colon as regards (1) stasis, (2) absorption of water and (3) bacterial flora. After periods varying between two and eight and one-half months, simple ileal obstruction was produced at the sites of the anastomoses. Three dogs survived for twenty-five, thirty-one and thirty-four days respectively. This period of survival is considerably longer than that of dogs with simple low ileal obstruction. A loss of 28 to 40 per cent of body weight occurred before death. Death was

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43. Sperling, L., and Wangenstein, O. H.: Effect of Previous Ileosigmoidostomy on the Survival Period of Dogs with Low Ileal Obstruction, *Proc. Soc. Exper. Biol. & Med.* **31**:323-326, 1933.

since been stressed by many investigators. These changes are usually attributed to the impairment of the circulation of blood to the intestine by distention. Most of the recent experimental work has dealt with the effect of distention of the bowel on the intestinal circulation. It has been demonstrated that the flow of blood is decreased as the pressure within the intestine is increased (Dragstedt<sup>24</sup>). Many investigators have referred to the damaging effect of increased intraenteric pressure on the intestinal wall. There has been no previous work establishing the exact level of the intraenteric pressure necessary to produce such changes. In most of the experimental work reported heretofore, extremely high pressures, much higher than those which occur in clinical cases of intestinal obstruction, were utilized (Gatch<sup>28</sup>). From this study it appears that definite pathologic changes can be produced in the wall of the intestine by sustained pressures which are much lower than those used by other investigators and which are comparable to the levels actually measured in experimental and clinical cases of intestinal obstruction.

Observations were made of the effect on the wall of the bowel of sustained and increased intraenteric pressure of the degree measured in experimental and clinical cases of intestinal obstruction. It was determined that diffusion of potassium ferrocyanide, strychnine or dyes through the wall of the intestine into the peritoneal cavity does not occur as long as the intestine remains viable. Although a pressure of 10 cm. of water sustained for twenty-four hours produces petechial hemorrhages in the wall of the intestine, the intestine remains viable and is impermeable to potassium ferrocyanide. Higher pressure (20 cm. of water) is, however, tolerated for only ten to twenty-two hours and results in congestion of the intestine. When this degree of pressure is sustained over a longer period (twenty-four hours) necrosis occurs and permeation of the necrotic areas by the test substances can be demonstrated. Still higher pressures (40 cm. of water or more maintained for eleven hours) result in hemorrhage, necrosis and loss of viability with permeation of the wall of the bowel. However, such pathologic changes are not regularly observed at autopsy after experimental simple ileal obstruction. This emphasizes the importance of the ability of the hollow muscular viscera, such as the bowel and the bladder, to accommodate themselves to alterations of volume without significant changes in the intraenteric tension. Undoubtedly the intestine is able to maintain, within certain limits, an adequate blood supply, despite the compression of the capillaries and of the small venules which follows the increase of intraenteric tension. This may be due to a dilation or stretching of the circular muscle fibers of the intestinal wall. Moreover the dilation of the intestine in experimental and clinical obstruction occurs so gradually that considerable distention may be present without a great increase of tension.



and Stone and Firor,<sup>5</sup> who have emphasized the importance of the lymphatics as an avenue for absorption in obstruction. However, severance of the mesenteric lymph pedicle in cats with intestinal obstruction to prevent absorption of toxins through the lymphatics did not lengthen the period of survival. Thus, no evidence was adduced to indicate that the occurrence of increased lymphatic absorption is of much significance in the causation of death of animals with intestinal obstruction.

This work emphasized the significance of the mechanical factors in simple intestinal obstruction. The ill effects of obstruction can all be traced to the effect of distention on the wall of the bowel. The factor of loss of fluid, while important in high intestinal obstruction, has been shown by other investigators to be unrelated to the duration of survival in cases of low ileal obstruction. The main consideration appears to be the viability of the intestinal wall. The normal intestine prevents transperitoneal migration of bacteria and of substances which are toxic when absorbed through the peritoneal cavity. A sustained high intraenteric pressure results in impairment of the viability of the wall of the intestine and thus allows transperitoneal absorption. Relatively low pressures (20 to 40 cm. of water) maintained over a sufficiently long period produce structural changes in the intestinal wall and allow this process to take place.

In view of what has been said in the previous sections on the effect of distention in simple ileal obstruction on the function and the structure of the wall of the intestine, the sequence of events in the development of the changes described may be summarized in the following manner: With the onset of intestinal obstruction there is stasis of fluid and gas within the bowel. The stasis produces a slight increase of intraenteric pressure and a moderate degree of distention, which stimulate the normal bowel to increased peristalsis. Distention and increased intraenteric pressure result in an augmented secretion of intestinal juices, which adds to the content of the bowel. Absorption is decreased early in the course of the obstruction. There is thus a progressive increase of distention and of intraenteric pressure. With a rise in intraenteric pressure there is eventually manifested interference with the circulation of blood to the wall of the intestine. Venous stasis ensues and causes infiltration of the intestinal layers with leukocytes. Eventually hemorrhagic infarction, necrosis and even perforation of the intestine may take place. If the intraenteric pressure is maintained over a sufficiently long time, the viability of the wall of the bowel becomes impaired and its permeation by toxic material may take place through the gangrenous patches. Death is then due to peritonitis or to absorption of toxic material by way of the peritoneum. Relatively low pressures (20 to 40 cm. of water) if

# INTESTINAL OBSTRUCTION

## EXPERIMENTAL EVIDENCE ON THE LOSS OF BLOOD IN INTESTINAL STRANGULATION

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MINNEAPOLIS

In the past, numerous attempts have been made to ascribe the disastrous effects of all types of intestinal obstruction to some one etiologic factor. Of the many explanations offered, that of intestinal toxemia has been given greatest consideration. Literally hundreds of investigators have tried to show that this or that toxin was the one responsible for the dire results. However, there has been no general agreement as to what toxin was to blame. This, together with the fact that no theory of intestinal toxemia has ever offered any benefit to the patient in the way of improved methods of treatment or lowered mortality, has cast grave doubt on this explanation. The work of the past thirty years, however, has shown that, from an anatomic and pathologic standpoint at least, intestinal obstructions can be divided into two major types or a combination of the two. The terms simple and strangulation obstruction have been used to designate and differentiate the two major forms by clinicians and investigators alike.

The first term, simple obstruction, implies an occlusion of the lumen of the bowel without gross interference with the mural blood supply, while the second, strangulation obstruction, implies a vascular impairment of the wall of the bowel and its mesentery. At operation or necropsy, patients for whom the diagnosis was made clinically not infrequently show some evidence of both types of obstruction. In fact, most strangulation obstructions are accompanied by a simple mechanical or neurogenic obstruction. The reverse is not usually the case. Occasionally, however, a simple obstruction may produce some intramural vascular changes, even to the point of necrosis and perforation of the intestinal wall. This is especially true when a so-called gas trap develops and produces stasis of blood within the wall of the bowel as a result of a pathologically high intrainestinal pressure. This occurs more frequently in the colon, where a neoplastic lesion of the sigmoid

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Abridgment of a thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery.

## METHOD OF EXPERIMENTS

In order to evaluate the role that the arteries and veins may play individually and collectively in determining the period of survival of dogs with strangulation obstruction, the experiments here reported were divided into four groups according to the type of strangulation produced. Variations in the length of intestine obstructed also were taken into account. In the creation of the various types of obstruction described in this paper,  $\frac{1}{4}$  to  $\frac{1}{2}$  grain (16 to 32 mg.) of morphine sulfate and  $\frac{1}{150}$  to  $\frac{1}{75}$  grain (0.4 to 0.9 mg.) of atropine sulfate were given preoperatively to each animal. Ether was used as the anesthetic in every instance, and sterile technic was employed throughout.

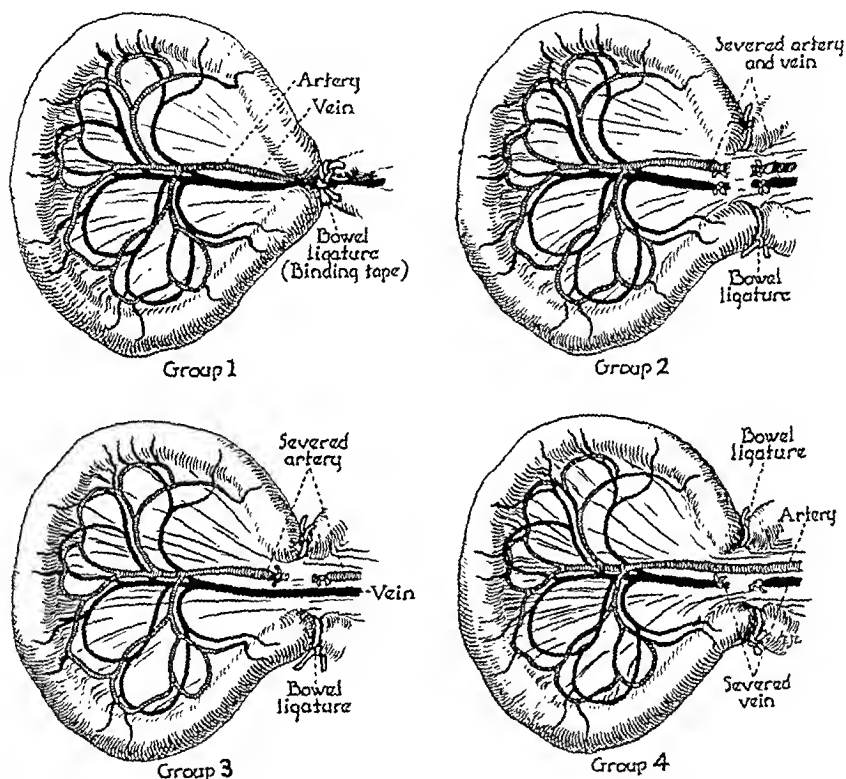


Fig. 1.—The four methods employed in producing the experimental strangulation obstructions recorded in this paper. Group 1 presents a partial occlusion of lumen and blood supply; group 2, a complete occlusion of blood supply; group 3, a complete arterial occlusion with patent vein, and group 4, a complete venous occlusion with artery intact.

*Type of Obstruction.*—In group 1 no attempt was made to control the relative degree of arterial or venous occlusion of the strangulated intestinal loops. In this way it was hoped that some idea might be obtained of the variations in length of life which one might encounter experimentally when a constricting band was passed about the mesenteric pedicle and the wall of the bowel. Binding tape, 1 cm. in width, was passed about the mesenteric vessels and then carried around the wall of the bowel and tied. The lumen of the bowel as well as its blood supply was thus occluded. The method is illustrated in figure 1. An experimental volvulus,

content of this fluid was usually less than 10 per cent. Examination of the bowel revealed it to be lusterless, dark purple or mahogany colored and moderately distended with bloody fluid when not ruptured. In this group and in the next (arterial obstruction), in which the pathologic findings were practically identical, 18 of 28 animals had loops which were ruptured in one or more places at the time of death. The wall of the intestine in these animals was usually thinner than normal, extremely friable and jelly-like. There were a few exceptions to these general statements. On 3 or 4 occasions, the intestine was found to be a patchy grayish yellow green; the wall was not perforated and the lumen not distended. This type of infarction was termed anemic

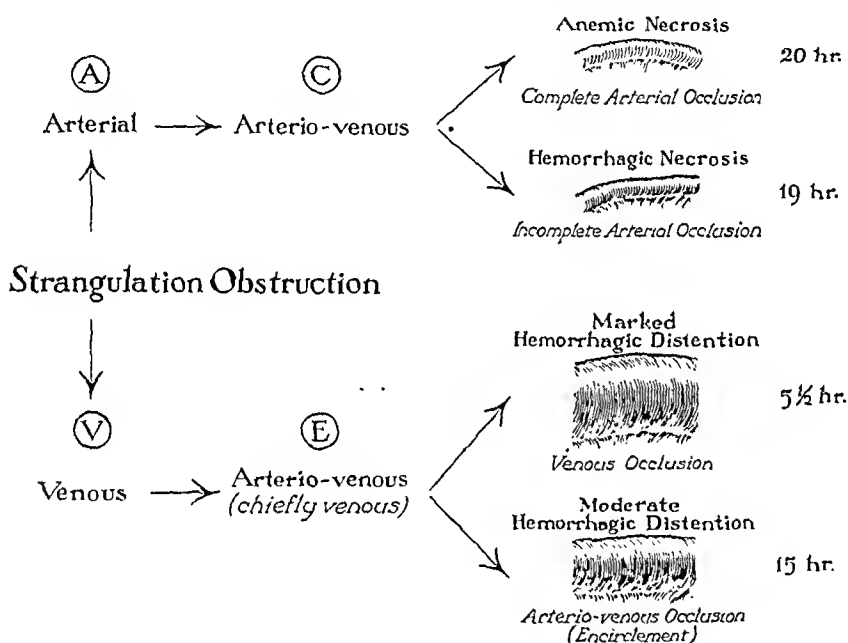


Fig. 2.—The various types of strangulation obstruction that may result, according to the relative degree of venous or arterial occlusion. When the arterial obstruction predominates there is little or no distention, whereas when the venous obstruction predominates there is a moderate to marked distention with blood.

necrosis, in contrast to the usual hemorrhagic necrosis seen in other types of strangulation. A careful analysis of the methods employed revealed the cause for the hemorrhagic necrosis in some instances and the anemic necrosis in others. In the cases of hemorrhagic necrosis blood apparently gained access to the wall of the bowel through the capillary bed of the mesentery proper, whereas no blood at all entered the bowel in the cases of anemic necrosis.

In group 3 (arterial obstruction), the pathologic picture, as previously stated, was practically the same as in group 2. In group 4, the

pathologic changes were almost identical with those in group 1, except that they were all more marked. The peritoneal fluid was present in larger amounts, the quantity ranging between 30 and 300 cc. The degree of distention of the bowel was likewise more marked. When the bowel was opened it was seen to contain rather large amounts of bloody fluid with a hemoglobin content ranging between 90 and 140 per cent (Sahli).

*Increase in Weight of Strangulated Loops of Intestine.*—When the strangulated bowels in groups 1 and 4 were weighed after the conclusion of the experiments, they were noted to have increased in weight over estimates based on a series of normal weights. The increase was from 133 to 235 per cent in group 1 and from 150 to 490 per cent in group 4. This increase was due solely to blood cells and plasma which had accu-

TABLE 1.—*Percentage of Increase in Weight of Strangulated Loops of Ileum in Eighteen Dogs*

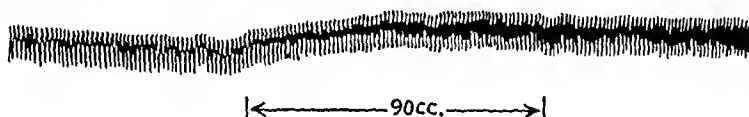
	Weight of Dog, Kg.	Length of Intestine, Ft.	Weight of Intestine, Gm.	Normal Weight, Gm.	Percentage of Increase in Weight
<b>Group 1 (encirclement of pedicle)</b>					
Minimum.....	11	2.0	240	76	133
Maximum.....	21	5.0	675	150	320
Average.....	15	3.2	460	103	235
<b>Group 4 (ligation of veins)</b>					
Minimum.....	8	3.0	260	90	150
Maximum.....	22	5.5	1,030	170	490
Average.....	15	4.3	680	135	233

mulated within the lumen and the wall of the intestine during the period of strangulation. Table 1 gives the minimum, maximum and average weights of strangulated bowels obtained at autopsy from a series of 18 dogs, 7 being in group 4 and 11 in group 1. The figures for normal weights of intestines are estimates based on tabulations of weights of given lengths of small intestine taken from 10 normal dogs. The average weight for 1 foot (30 cm.) of normal ileum was found to be approximately 30 Gm. and 1 foot (30 cm.) of normal jejunum 35 Gm. Table 1 shows in percentage the increase in weights of strangulated loops of ileum in 18 dogs.

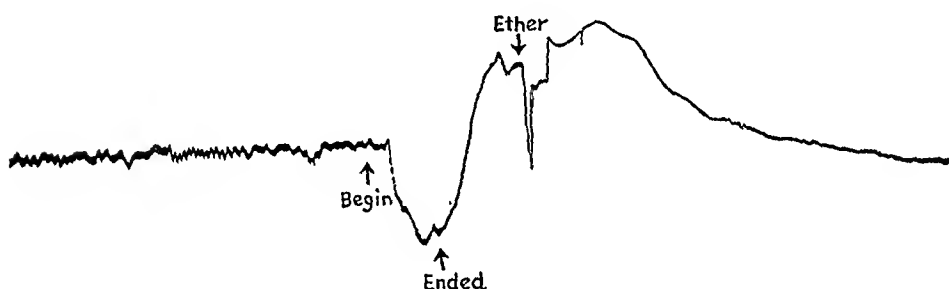
*Total Protein Content of Peritoneal Fluid.*—From the gross pathologic condition of the bowels, the microscopic picture and the increase in weight of the intestine, it was evident that a rather large amount of blood was lost into the lumen and the wall of the bowel. This was especially true in the group with patent arteries and ligated veins. The peritoneal cavity, as already noted, was observed to contain a moderately large amount of clear blood-tinged fluid. Calculations of total protein content of the peritoneal fluid were made in three of the groups,

infection. Three of these 4 had received peritoneal fluid obtained from animals in which the loop had ruptured prior to death. The fourth animal from which peritoneal fluid had been taken died with an intact loop, but the wall of the intestine was necrotic. The peritoneal fluid obtained from this animal, as well as that from the 3 with ruptured loops, had a foul odor, and bacteriologic studies revealed the presence of innumerable bacteria, both anaerobic and aerobic.

In the 10 animals that showed no immediate effect other than a slight rise in blood pressure there was likewise no delayed effect. Within an hour or two after the discontinuance of the anesthesia, the animals



A



B

Fig. 4.—*A*, effect on the carotid blood pressure of a normal dog of injecting intravenously 90 cc. of peritoneal fluid from a dog with a strangulation obstruction (encirclement) of eighteen hours' duration. The strangulated loop of bowel was not grossly ruptured. The recipient suffered no immediate or delayed effect. *B*, effect on the carotid blood pressure of a normal dog of injecting intravenously 40 cc. of peritoneal fluid from a dog with a strangulation obstruction (ligation of arteries and veins) of fifteen hours' duration. The strangulated loop was grossly ruptured. The recipient died by the following morning.

were up and about as usual. The next day they ate well and appeared normal in all respects. The tracings shown in figure 4 are typical of the effects which have been described. From these experiments it may be concluded that the peritoneal fluid when injected intravenously has no appreciable effect on the blood pressure or general health of the

In group 1 (by strangulation encirclement), 3 experiments were carried out. One hundred and fifty milligram doses were employed. In all 3 animals convulsions were delayed. In the first animal convulsions developed in about four hours, and death ensued in four and one-half hours. The second and third animals died in convulsions after seven and fifteen hours respectively. The first signs of irritability or convulsions appeared just a few hours prior to death. These results indicate a great delay in absorption as compared with the normal rate. The wide variation in time of development of symptoms was to be expected in this group in view of the fact that no attempt was made to arrest the flow of blood completely, the degree of occlusion depending entirely on the tightness of the encircling tape. The peritoneal fluid was tested for the presence of strychnine after the death of the animal by the injection of 2 to 5 cc. samples of it into the dorsal lymph sacs of frogs, which were then observed for tetanic convulsions. None of the frogs gave a positive reaction, except that in which the sample obtained from the animal that died after fifteen hours had been injected. This animal had a grossly perforated loop, and it was to be expected that its peritoneal fluid would contain strychnine.

In group 2 (complete strangulation), 10 experiments were carried out. Six animals showed no sign of convulsions, while delayed convulsions developed in 4. Death occurred in these animals after six, seven, twelve and fourteen hours respectively, and convulsions were first observed in each instance only an hour or two before death. When the peritoneal fluid from these 4 animals was tested by injection into frogs, the presence of strychnine was indicated only in the postmortem specimen from the animal that died after twelve hours. Of the 6 animals that died without tetany or convulsions, the same test indicated the presence of strychnine in the postmortem specimen from only 1, which had lived thirty hours after strangulation. The strangulated loop in this animal was extremely necrotic and friable but not grossly perforated. In group 3 (arterial obstruction), 10 experiments were carried out. None of the 10 animals showed signs of strychnine poisoning. There was some evidence of minute amounts of strychnine in the peritoneal fluid, as convulsions developed in from twelve to forty-five minutes in 3 frogs into which it was injected. In group 4 (venous obstruction), 9 experiments were carried out. Convulsions developed in 3 of the 9 animals. The explanation for these results was evident at autopsy, when the normal adjacent intestine was seen on being opened to contain bloody fluid from the strangulated loop.

Although these experiments might seem to indicate that toxic products can be absorbed from the strangulated bowel, one must remember that when convulsions did occur they were greatly delayed. Moreover, as pointed out in reference to the last group, the possible avenue of

all the evidence in this and the preceding section would point to a delay rather than an acceleration in absorption from the damaged wall of the bowel. Furthermore, the devitalized wall of the bowel is apparently impermeable to tetanus toxin, at least over a twelve hour period.

*Intraperitoneal Autolysis of Autoclaved Intestine and Intestine Treated with Chemical Antiseptics.*—In order to determine whether the wall of the bowel itself is "toxic," an attempt was made to free the normal intestine of the dog from its usual bacterial flora by chemical and thermal sterilization. Segments of bowel thus treated were placed in the peritoneal cavities of normal dogs, in order to determine their relative and actual degree of "toxicity," as judged from a clinicoexperimental standpoint. In every instance in which segments of intestine were treated with chemical antiseptics for periods varying from five to ten minutes, cultures of mucosal scrapings were observed to contain a great variety of organisms. When these chemically treated loops were

TABLE 4.—*Resulting Mortality in Twenty-Eight Dogs When Segments of Small Intestine Obtained from Other Dogs Were Treated in Various Ways and Introduced into the Peritoneal Cavity*

Number of Experiments	Method	Percentage of Mortality
2	Open loops of ileum, devascularized.....	100
3	Open loops of jejunum, devascularized.....	100
2	Devascularized Thirty-Vella loops.....	100
4	Segments of bowel treated with tincture of iodine.....	100
4	Segments of bowel treated with mercurochrome and alcohol.....	75
3	Segments of bowel treated with water and ether.....	100
10	Segments of bowel autoclaved 30 to 45 minutes.....	10

placed in the peritoneal cavities of 18 normal animals, only 1 survived. In contrast to this, 9 of 10 animals survived that had loops of bowel sterilized by steam placed in their peritoneal cavities. Cultures of the mucosa from the autoclaved loops were negative in all instances. A few organisms must have been present in the mucosa of the bowel in 1 case or have gained entrance at the time of operation, as the animal died five days later of bacterial peritonitis. These results were to be expected in view of the fact that the devitalized intestine and the peritoneal cavity provide bacteria with an ideal culture medium under optimum temperatures. This work substantiates the experimental results of Dragstedt<sup>8</sup> and his co-workers, who showed that it was extremely difficult to sterilize the normal bowel with the usual antiseptics. It also confirms their conclusion that devitalized sterile loops of bowel are harmless.

8. Dragstedt, L. R.; Dragstedt, C. A.; McClintock, J. T., and Chase, C. D.: Intestinal Obstruction: II. A Study of the Factors Involved in Production and Absorption of Toxic Materials from the Intestine, *J. Exper. Med.* **30**:109, 1919. Dragstedt, L. R.; Moorehead, J. J., and Burcky, F. W.: Intestinal Obstruction: I. An Experimental Study of the Intoxication in Closed Intestinal Loops, *ibid.* **25**:421, 1917.



of mercury and the highest 140 mm. In 7 dogs, in which the length of intestine was less than 3 feet (90 cm.), the blood pressure had not fallen in any case below 100 mm. In the 9 remaining dogs, in which the segment strangulated was more than 3 feet (90 cm.) in length, the pressure at the time of release was less than 100 mm. in 6 instances. The time at which the release was effected varied within each division of this group, but the interval was approximately the same in both divisions, with but 1 exception. In group 2, in which the arteries and veins were ligated, the pressure was found to be within normal limits after from four to six hours' observation. Also in group 3, in which the arteries were ligated, the pressure was found to be within normal limits after from four to six hours. Tracings were taken after eighteen and one-half hours in the case of 2 animals which appeared moribund at that time. One showed a mean pressure of 20 mm. and the other of

TABLE 5.—*Decline in Hemoglobin Content of the Blood of Three Dogs in Which Strangulation Obstruction of the Small Bowel with Ligation of the Veins Was Produced*

Dog 303		Dog 304		Dog 305	
Time	Percentage of Hemoglobin	Time	Percentage of Hemoglobin	Time	Percentage of Hemoglobin
8:30 a.m.	103	8:15 a.m.	106	10:00 a.m.	95
9:10	Strangulation	9:50	Strangulation	10:30	Strangulation
9:40	103	10:20	96	11:00	84
10:40	105	11:20	102	12:00 noon	70
11:40	102	12:20 p.m.	78	12:50 p.m.	68
12:50 p.m.	90	1:20	65	1:50	65
1:50	82	2:10	Resection	1:40	Resection
2:50	76	2:20	68	2:50	62
3:35	Dog dead	3:25	70	3:50	63

70 mm. The first died half an hour later and the second one and one-half hours later; these observations signify that, though it was delayed, there was a definite fall in blood pressure terminally. In group 4, consisting of 10 dogs in which the veins were ligated, the pressure was below 70 mm. in every instance after from one to five hours. Three of the 10 animals were dead within this time. One animal, in which the superior mesenteric vein was ligated, died within one hour. Two of 3 dogs in which the veins to a 5½ foot (170 cm.) segment were ligated died within four hours, with consistent decline in blood pressure during the course of the experiments. One animal in which the veins to a 5 foot (150 cm.) segment were occluded was still alive at the end of four hours but had a blood pressure of only 54 mm. The remaining 6 dogs, in which veins were occluded to a segment of less than 3 feet (90 cm.), were all alive after an interval varying from three to five and one-half hours.

In several instances the pressure within the mesenteric veins to the loop of intestine selected was measured while a venous obstruction

*Period of Survival After Various Types of Obstruction.*—The four usual types of obstruction were produced in a number of instances with a view to determining the average length of life in the various groups. The lengths of bowel strangulated were varied in order to determine the variations which might result in accordance with the observations of Foster and Hausler.<sup>9</sup> In the experiments of group 1, in which an encircling ligature was placed about the mesentery and bowel in 14 dogs, the period of survival varied between four and twenty-eight hours. The mean length of life was sixteen hours. The length of bowel strangulated varied between 1 and 5 feet (30 to 150 cm.). The dog with the shortest obstruction lived the longest, an observation which is in accordance with Foster and Hausler's views. However, the dog with the longest obstruction lived longer than a number of other dogs with shorter obstructions. This and other exceptions to Foster and Hausler's conclusions were anticipated in view of the fact that the relative degree of arterial and venous obstruction could not be accurately controlled in this group. Further, the animals varied in weight as well (10 to 25 Kg.). Therefore, the actual length of intestine obstructed gives no indication of the relative amount obstructed, which is actually of greater significance. In 18 experiments of group 2, in which the arteries and veins were completely ligated, the shortest period of survival was eleven hours and the longest thirty-two. The length of intestine strangulated varied as in the preceding group between 1 and 5 feet (30 to 150 cm.). The mean length of life for this group was nineteen hours. In group 3, in which the arteries were tied in 9 dogs, the shortest period of survival was fifteen hours and the longest twenty-four hours. The length of bowel strangulated varied between 1 and 4 feet (30 to 120 cm.). The mean length of life was twenty hours. In group 4, in which the veins were tied in 15 animals, the shortest period of survival was two and one-half hours. The length of intestine varied between 3 and 5½ feet (90 to 170 cm.). The mean length of life was five and one-half hours.

Examination of table 7 reveals that the length of life in group 4, in which venous obstruction was produced was approximately one-fourth that in group 3, in which the arteries were obstructed, and in group 2, in which combined ligature of arteries and veins was performed; it was approximately one-third that of group 1, in which the degree of arterial occlusion was not absolute in all cases. Although the length of bowel involved is of great importance in shortening or prolonging the period of survival after strangulation obstructions, the type of obstruction seems to be of even greater significance, as a pure venous obstruction causes death in one-fourth the time that an arterial obstruction does.

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9. Foster, W. C., and Hausler, R. W.: Studies in Acute Intestinal Obstruction: II. Acute Strangulation, *Arch. Int. Med.* **34**:697 (Nov.) 1924.

normal value. Consequently no values for increase in the weight of the intestine are listed for these two groups. In the instances in which the loop was ruptured, the peritoneal cavity contained large amounts of peritoneal fluid of high total protein content, the values ranging from that of the animal's own blood plasma up to twice that amount. In a few instances in which the loop was not ruptured the peritoneal fluid had a total protein content less than that of the blood plasma. The amount of fluid noted in the peritoneum was calculated to be 22 per cent of the total blood volume in the second group and 20 per cent in the third group.

In group 4 (venous ligation), symptoms of shock resulted relatively early and were soon followed by death. Within two hours, the animals began to show a definite increase in the respiratory and cardiac rates, and

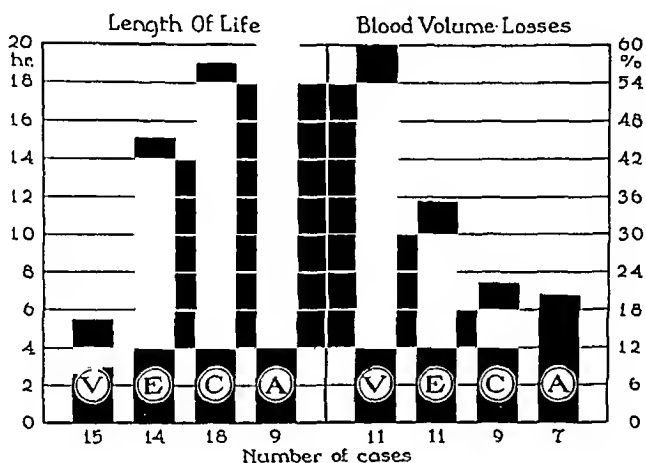


Fig. 5.—The correlation between loss of blood volume and length of survival in dogs with the various types of strangulation obstruction; V = venous; E = encirclement; C = complete; A = arterial.

the hemoglobin content had begun to fall, as had the blood pressure. In a few animals in which the abdomen was opened after this interval, the strangulated intestine was seen to be of a dark mahogany color, lusterless and distended, as previously reported. All these conditions were minimal shortly after the strangulation was produced and increased during its course, reaching a maximum at the time of death. Deaths in group 4 occurred after a loss of from 34 to 66 per cent of the total blood volume. The average for the group was 55 per cent, and the average length of life was five and one-half hours. Losses in the blood volume were calculated as in group 1. A summary of the data will be found in table 8. The rapid fall in blood pressure, early shock and death in group 4 (venous obstruction) were associated with a loss of

Death will occur relatively late and will be secondary to a loss of plasma into the peritoneal cavity and an absorption of bacterial toxins therefrom. If, on the other hand, the venous occlusion predominates in the face of normally patent, pumping arteries, or even partially patent arteries, the result will be a loss of whole blood into the wall and lumen of the bowel and a transudation of plasma into the peritoneal cavity, associated with a distention of the strangulated loop, varying from a moderate to a marked degree.

Of clinical interest is the fact that shock and death result early after pure venous obstruction only when the strangulated intestinal loop is adequately long, or when no egress of blood can take place into the lumen of the adjacent normal bowel to relieve the intraluminary pressure of the strangulated loop. In many clinical cases, an egress of blood does occur into the normal adjacent bowel, and the rate at which blood is lost most likely depends on the degree of obstruction of the lumen of the bowel and on the resulting intraluminary pressure.

#### SUMMARY

The results of 240 experimental strangulation obstructions are herewith presented. They seem to show that a loss of whole blood and plasma is an important contributing factor to the development of shock and even of death. The gross pathologic picture, as well as the microscopic observations, indicates a loss of whole blood into the wall and lumen of the strangulated loop of the bowel.

The type of strangulation produced is found to be dependent on the relative degree of venous or arterial occlusion. When venous occlusion predominates the loss of whole blood is the chief factor, and when arterial occlusion predominates the loss of plasma is important. Tables are presented which show that there is a marked increase in the weight of the strangulated bowel over the normal weight. This increase in weight has been found to be due to the accumulation of blood in the wall and lumen of the strangulated loop of the bowel. Determinations reveal that the material within the loop has a high hemoglobin content and that the free peritoneal fluid is similar in total protein content to the animal's own blood plasma.

The loss of blood in strangulation obstructions has been calculated and found adequate, with the venous types of occlusion at least, to account for the shock and death which occur. Experiments presented tend to show that the blood pressure falls rapidly and the hemoglobin content drops rather uniformly. Experiments are also presented which show that the fall in blood pressure depends on the length of intestine involved and on the predominate type of strangulation produced.

Experiments are presented to show that "toxic products" are not present in the peritoneal fluid except terminally when the loops are

# OSTEOGENIC SARCOMA

## A REPORT OF TWO UNUSUAL CASES

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I have been fortunate in observing two interesting cases of osteogenic sarcoma in the past five years, and I submit the records in detail:

### REPORT OF CASES

CASE 1.—J. S., a girl aged 13, was first seen in April 1932. The mother stated that several months previously her daughter had fallen, striking her right knee. Sometime later the child began to limp and to complain of pain in the leg. A swelling appeared above and to the outer side of the knee, and the patient was taken to the General Memorial Hospital where she was examined. A diagnosis of osteogenic sarcoma was made, and the family was advised that an amputation was imperative. The parents refused to consent, and a short while later the child was brought to my office.

After having some roentgenograms taken, I made a diagnosis of osteogenic sarcoma and advised amputation (fig. 1). A second refusal led me to plead for local excision, and this was granted. Part of the growth was removed at the Columbus Hospital Extension on May 23, 1932, and the pathologic report of Dr. A. Sala stated that the growth was a rapidly growing osteogenic sarcoma.

Still the family refused consent for an amputation. My only recourse, in the hope of retarding the growth, was to give a series of injections of Coley's toxin. Injections were given locally and in the buttocks for nearly a month, but were of no avail. The pain and limp increased, and the growth soon reappeared locally.

A roentgenogram at this time showed the growth to be as large as ever (fig. 2). Finally the parents consented to an amputation, which was done through the upper third of the thigh on July 17, 1932, at Bellevue Hospital.

The pathologic report, made by Dr. McWhorter, was as follows: "The specimen consists of the lower end of the femur, which has been split longitudinally (fig. 3). On the popliteal surface, just proximal to the epiphysial line, is a fusiform growth of dense consistency. This growth involves the medullary cavity and appears to be growing outward. Microscopic examination shows a densely infiltrating mass of undifferentiated connective tissue cells of short spindle type. Scattered throughout the sections are many giant cells of tumor type" (fig. 4).

Since the operation the patient has slowly recovered, but she has been kept under observation. She has not gained much weight, but periodic roentgenograms of her chest and long bones show no metastases. During the past year she has had

trouble with her stump. It has become quite swollen, and she has not been able to wear an artificial limb. A plastic revision was done in April 1936, and a fairly large slice of skin and fat was excised. No evidence of any soft local tumor recurrence was found.



Fig. 3 (case 1).—Cross-section of the specimen.

CASE 2.—E. D., a boy, a patient of Dr. D. Zetena, was admitted to the Columbus Hospital Extension Nov. 26, 1934, and was discharged Jan. 27, 1935.

The history given was that while passing through a door of a train on Sept. 30, 1934, the child was pushed by the crowd so that his right foot was caught between the platform and the train and he fell onto the platform, striking his right thigh. From that day on he complained continuously of pain, and his mother noticed a swelling on the right thigh, which was soft, was not red and did not fluctuate.

Physical examination revealed nothing abnormal except the painful swelling in the upper part of the right thigh. There had been no previous illnesses except pneumonia at the age of 8 months and otitis media at 1 year.

The blood count on admission showed 13,000 white cells, with 52 per cent lymphocytes and 37 per cent neutrophils. The urine was essentially normal.

Roentgen examination of the right femur showed slight irregularity of the periosteal shadow along the anterior and lateral borders of the upper third of the shaft of the femur, the changes beginning slightly below the greater trochanter and extending downward about 3 inches (9.5 cm.). The periosteum was slightly elevated in the upper and lower portions. There were fine radiating lines extending at a right angle from the cortex into the soft tissue. There was no definite



Fig. 5 (case 2).—Early osteogenic sarcoma with sun ray bony growth into the soft parts.

involvement of the cortex or medulla. The changes had the appearance of a periosteal osteogenic sarcoma (fig. 5).

On Dec. 1, 1934, the patient was ready for disarticulation at the hip; so a preliminary histologic examination of a portion of the periosteum was made, and a frozen section showed a sarcoma. Thereupon disarticulation was carried out.

Two curved incisions were made starting about the center of Poupart's ligament, one going outward and the other inward, both meeting behind near the middle of the gluteal fold. The femoral vessels were exposed and doubly ligated with chromic catgut. The adductor and abductor muscles and hamstrings were severed close to their origin. An injection of 90 per cent alcohol was made into the sciatic nerve, as located, and the nerve was cut high up. The capsule of the joint was incised, the ligamentum teres clamped and divided and the head of

## COMMENT

The first case is reported because of the extraordinary fact that after a rapid local recurrence of the growth following the initial operation, and after repeated injections of Coley's serum which did not help the condition, an amputation was done. At the present time, after an interval of five years, there has been no reappearance of the tumor in the stump or in any other part of the body.

The second case is of interest in view of the fairly definite history of trauma, the uncommon location of the growth and the fact that the child could stand the shock of a radical disarticulation of the hip. This patient has gone over two years without recurrence or metastases.



mental physiological functions of the body, that is to say, Innervation, Capillary Circulation, Nutrition and Secretion, and we shall find that inflammation always involves a deviation from the normal condition of every one of these functions.

While there may be lesions of any one of these functions, or of several of them, without inflammation, this *always* exists when the whole are affected. And yet inflammations are not always alike; they differ infinitely according to their cause and to the structure invaded.

Inflammatory affections, so called, are therefore as numerous and as various as the diseases classed under this head. No two are alike in their manifestations, nor in their history. They differ in causation, in symptoms, in duration, in terminations and in curability. They are therefore strictly speaking, entities; and should be more generally admitted to be so. If this general assent could prevail we might dispense with the word inflammation, and allow each entity or disease to be judged and treated according to its own or individual peculiarities. But the word has been so long in use, and is so intimately interwoven with our facts as well as theories, that we may not expect to see it set aside in our generation, nor probably in several more of them. With this explanation, I will continue its use as a matter of convenience whenever it answers the purpose.

Is inflammation curable?—This may strike some as a ridiculous question, for it is in striking contrast with the dogmatic declarations of every period of the history of medicine. To intimate any doubt as to the efficacy of the modes of treatment advocated by leading men from Hippocrates to Broussais, would seem to be as preposterous in Medicine as heresy in theology. And yet the extravagancies of Broussais aroused a spirit of inquiry so potent that he lived to see his favorite dogmas, first doubted, and then almost unanimously discarded by the profession. His hobby that by depletion all inflammations could be readily "removed," has now become obsolete, and every one knows that you may draw blood "*ad deliquium animi*" without curing a simple pimple on the face, and that the same inefficiency attaches to any other form of antiphlogistic treatment. I wish it to be borne in mind that I use the term *cured* in its strict sense; that is to say, that the inflammatory process was found to pursue the even tenor of its way in despite of any known form of treatment.

As it was my good fortune to be at the seat of war whilst it progressed most furiously between the friends and adversaries of the Broussaisian School, I had abundant opportunities to verify the claims of the respective parties; and became satisfied that the victory was with the opposition, and that inflammation could not be *cured* by antiphlogistics, nor by any other plan of treatment then known. Whenever the inflammation was on the surface, so as to be seen in its various stages, it was never arrested by treatment; but ran its peculiar regular course to resolution or to some other of its accustomed terminations. Such being the case with regard to inflammations subject to ocular inspection, we could not reasonably suppose different results in the progress of inflammations affecting internal organs.

Such are the doctrines I continued to teach until about ten years ago; and the object of this paper is to lay before you how my views have undergone a change.

As far back as the introduction of Quinine in the treatment of our malarial fevers, which were then considered inflammatory, and treated as such, I was forcibly impressed by the prompt and certain arrest of the disease by this wonderful agent. Could it be that quinine arrested inflammation?—or had we been in error with regard to the pathology of our fevers?—The organs apparently implicated were out of sight, and we might have mistaken hyperaemia for inflammation. I became convinced that such was the fact, and the efficacy of Quinine

I have found Tincture of Iodine sometimes beneficial, but not so in the thecal and periosteal varieties. For buboes, whether syphilitic or otherwise, I have no reason to think it prevents or lessens the tendency to suppuration; indeed I am rather disposed to think I have seen suppuration oftener when it was used than when I resorted to other expedients. This may appear singular when we remember how valuable an agent the Tincture is in dispensing some of the chronic enlargements of lymphatic glands.

We have endeavored to demonstrate; first, that no *definition* of the word inflammation hitherto proposed is satisfactory.

Secondly, that the so-called inflammation is a radical perturbation of the fundamental physiological functions, which varies according to its cause and the tissues involved;

Thirdly, that inflammations should be regarded and treated as entities, or distinct diseases;

Fourthly, that when I commenced my professional studies it was generally conceded that inflammatory affections were curable;

Fifthly, that the ultraisms of Broussais instigated a spirit of inquiry which resulted in the conviction that no treatment then known could be said strictly to cure or to arrest the regular progress of inflammatory action;

Sixthly, that this conviction became, with me, somewhat shaken by the introduction of quinine;

And finally, that it is now demonstrated beyond doubt that some of the forms of inflammation may be effectually arrested by the application of tincture of iodine to the affected locality.

It has been wisely stated that there is nothing new under the sun, and I shall therefore not lay claims to originality which might be controverted by the more erudite; but I must say that my first use of Tincture of Iodine, as above narrated, was not instigated by knowledge derived from others—If others had done the same before I was not aware of the fact.

I have ventured to place this paper at your disposal because I regard the discovery—by whomsoever made—of the fact, that some forms of inflammation are undoubtedly curable, as one of the utmost importance. It not only corrects one of the convictions of the learned, but must lead to farther discoveries in the same direction. As one step in advance is only the precursor of others, let us redouble our exertions, in the hope that some one among us may have the honor of contributing the next fact.



Steps in the operative technic. The gallbladder is first aspirated, as in *A*, and the fundus is incised, as in *B*. After the fundus is incised, the stones are evacuated, the gallbladder is dried out and swabbed with tincture of iodine and is split down to the cystic duct. After the removal of any stone at the junction of the ampulla and the cystic duct, the redundant portion of each half is trimmed off with scissors, leaving only that portion of the gallbladder attached to the liver, as in *C*. The cut margins of this remnant of the gallbladder are sutured to the liver, as in *D*. Cigaret drains are placed about the cystic duct and against the remnant of the gallbladder to hold it open, as in *E*.

Also, two of the five patients requiring dietary restrictions have had transitory symptoms of jaundice, epigastric pain and vomiting at long intervals. One of these has remained free from symptoms for eight years and now has diabetes. Another patient had ten stones removed from the common duct coincident with partial cholecystectomy, but as a rule simultaneous exploration or operation on the common duct is rarely advisable when extensive induration and inflammation are present about the duct because of the added operative risk and excess trauma due to the technical difficulties of exposure and control of hemorrhage and infection. Ordinarily, if the involvement of the common duct is definite at the time of partial cholecystectomy, a two stage procedure had best be planned.

3. *Fate of Remnant of Gallbladder Allowed to Remain.*—I have had the opportunity to reoperate on three patients. Two required hysterectomy, and the area of the gallbladder was simply palpated. There were dense adhesions to the fossa of the gallbladder, but no evidence of any thickening to suggest reformation of the gallbladder. The third patient had to undergo choledochostomy for the removal of 5 stones eight years after the partial cholecystectomy. There were adhesions of the gastrocolic omentum and thickening of the capsule of the liver over the fossa of the gallbladder but no vestige of anything that even resembled the gallbladder or a remnant of the gallbladder.

*Postoperative Hernia.*—As extensive drainage is necessary in partial cholecystectomy—at least three drains are usually required—postoperative hernia might readily be expected, except in those cases in which the drains are brought out through a lateral stab incision. In my series of cases, an opening in the fascia at the point of drainage could be palpated in most of the scars, but in only six of the cases (14.3 per cent) was there definite hernia—that in an obese man of 76 was large and gave symptoms of obstruction, but he has consistently refused operative relief.

*Miscellaneous.*—In three cases diabetes developed from three to eight years after operation. In one a keloid occurred in the scar. Six patients have died of disease unrelated to the biliary passages or liver from one and one-half to twelve years subsequent to operation.

#### REVIEW OF LITERATURE

Partial cholecystectomy is not a new procedure. In 1899 and again in 1900 W. J. Mayo<sup>2</sup> reported cases, particularly of obstruction of the cystic duct, in which the removal of stones and the mucous membrane

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2. Mayo, W. J., and Mayo, C. H.: A Collection of Papers, Published Previous to 1909, Philadelphia, W. B. Saunders Company, 1912, vol. 1, pp. 348 and 355.

In 1927 Gatch<sup>8</sup> and also Zimmerman<sup>9</sup> reported a similar technic.

In performing partial cholecystectomy for gangrenous cholecystitis, Haggard<sup>10</sup> (1930) destroys the mucosa of the remaining portion of the gallbladder either with phenol or with actual cautery, inserts a tube into the cystic duct for drainage and sutures the cut edges of the gallbladder over it.

McKenty<sup>11</sup> (1933), in reviewing the treatment for acute cholecystitis, cited thirty-three cases in which partial cholecystectomy was performed, with one death. After aspirating the contents of the gallbladder, he opens it, removes the stones and swabs the gallbladder with iodine, leaving an iodine pack in "the sac," and exposes and ties the cystic duct and artery. "The sac is then excised either from above downward or from below upward, leaving the portion attached to the liver undisturbed. From this portion the softened mucosa is easily removed by rubbing with gauze preferably saturated with iodine."

Ritchie<sup>12</sup> (1937), after splitting the gallbladder and excising the "wings," removes the mucous membrane of the portion allowed to remain, sutures a tube into the stump of the ampulla and cystic duct and closes the denuded fragment of the gallbladder by suture. He reported sixteen cases in which this procedure had been used, with no mortality.

#### SUMMARY

It must be understood that this operation would seem to be particularly applicable in cases of acute suppurative or gangrenous cholecystitis or empyema of the gallbladder, especially when there is induration about the cystic and common ducts, and occasionally for the small, densely adherent, thickened, atrophic gallbladder which cannot be easily separated from the bed of the liver. In no way should partial cholecystectomy be considered to supplant complete cholecystectomy when complete removal can be safely accomplished. The operator who is exceptionally skilful in the use of cholecystectomy from above downward may find less use for partial cholecystectomy than one whose proficiency has been directed to cholecystectomy from below upward. Furthermore, though cholecystostomy must still be reserved for the patient who is an exceptionally bad risk, fewer cholecystostomies seem indicated when familiarity with partial cholecystectomy has been acquired.

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8. Gatch, W. D.: *Tr. West. S. A.* **37**:345, 1927.

9. Zimmerman: *Tr. West. S. A.* **37**:341, 1927.

10. Haggard, W. D.: *Wisconsin M. J.* **29**:683, 1930; *Ann. Surg.* **105**:790, 1937.

11. McKenty, J.: *Canad. M. A. J.* **33**:771, 1933.

12. Ritchie, H. P.: *Surgery* **1**:581, 1937.

The large, edematous, water-logged gallbladder renders isolation of the cystic duct difficult. Removal of the gallbladder, even from above, entails considerable risk of injury to the deeper ducts. Of all things that one wishes to avoid, that evil result is the least desirable. Partial cholecystectomy will obviate that danger. In the large gangrenous gallbladder which is so friable one can scarcely handle it without rupture and soiling, aspiration and adequate tamponade are essential.

Excision of the diseased or gangrenous wall of the gallbladder leaves the part that is embedded in the fossa of the liver. Having the best circulation on account of its attachment to the liver, it is rarely gangrenous. One need not be afraid of the little part that is left. The surgeon is so imbued with the idea that he must take out every particle of the gallbladder that he is fearful about leaving any part of it.

After the stone or stones and the liquid contents have been removed, the walls of the gallbladder are cut away. Removal of the remnant adherent to the liver is often a bloody procedure and leaves a large raw bleeding surface that is difficult to suture. Multiple drains are usually required. The little piece of gallbladder adherent to the bed of the liver is the patient's protection.

One can remove the mucosa by rubbing it with gauze. Swabbing with phenol will denude it, and the acid is then neutralized with alcohol. Destruction of the mucosa will do away with secretions, and no sinus will result.

The cut edges of the remnant of gallbladder are sewn over a catheter in the cystic duct. Drainage is adequate. It is a most satisfactory way to get out of a difficult situation and avoid adhesions.

DR. DONALD GUTHRIE, Sayre, Pa.: I agree that the operation Dr. Estes has described is the correct one to employ in these desperate situations instead of the more radical operation of cholecystectomy.

The surgeon should use his best judgment in the selection of cases of cholecystitis for operation during the acute phase of the disease, for in spite of all that has been said lately about the need of prompt operation to prevent perforation or gangrene, the tendency is toward conservative treatment. Neither gangrene nor perforation of the gallbladder are feared as much in cases of cholecystitis as in cases of acute appendicitis.

My associates and I have practiced in a measure the plan suggested by Dr. Estes. We remove the mucous membrane and leave the serosa behind, for infection cannot recur in a hollow viscus if the mucous membrane is removed or destroyed.

This procedure is called a compromise cholecystectomy. After the contents of the gallbladder are aspirated and the gallbladder is opened, the organ is split from the fundus to the infundibulum, the margins are widely retracted and the thickened mucous membrane is separated from the cut edges with the handle of the scalpel.

After the mucous membrane is well separated from these edges, it is usually easy to complete its removal with finger dissection. Bleeding vessels are ligated, excess serosa is cut away and the edges are sewed together over a small rubber tube.

It is usually impossible to bring the edges of the liver together after complete removal of a large gallbladder, because the thickened posterior layer of the serosa generally comes away with the gallbladder, and it is often necessary to pack the bed of the liver with gauze to control the bleeding. This is dangerous.

Poor exposure, improper mobilization of the infundibulum and hemorrhage from the cystic artery are frequent causes of injury of the common duct, with the development of a postoperative biliary fistula or a stricture of the common duct.

# FRACTURES OF BOTH BONES OF THE LEG

## MANAGEMENT BY USE OF THE DOUBLE STEEL PIN TRACTION IN PLASTER OF PARIS

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AND

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This paper is a summary of the treatment, progress and results of treatment of tibiofibular fractures in 23 consecutive cases managed by the traumatic surgery staff at the Hurley Hospital between Jan. 24, 1935, and Jan. 29, 1937. We have had 7 more cases since the last-named date, but we consider these too recent to be useful in drawing definite conclusions. However, thus far the course has been comparable to that in cases in which we have been able to collect more nearly complete data. In addition, other surgeons on the hospital staff have had 17 cases, which are also not included in this series. Results have been uniformly good as far as can be ascertained.

Enthusiasm for the acceptance of the method of management of tibiofibular fractures by means of the double steel pin came as a result of the work of Dr. R. A. Griswold, of the department of surgery of the Louisville City Hospital and University of Louisville School of Medicine, who described the routine procedure, after-care, results and conclusions in the management of 43 fractures of this nature. The results were considered excellent, and one of us (Curry) decided to adopt the method. While a series of 23 cases may appear rather small, the results obtained seem to justify a report at this time.

In the short period of two years the fundamental principle of traction by steel pins, one through the os calcis and the other through the tibia posterior to the tibial tubercle, has been changed only by the availability at present of specialized apparatus for gaining the approximation of the bone fragments.

In this clinic the *indications* for the use of the double steel pin method of traction and immobilization in plaster of paris for combined fractures of the tibia and fibula are (1) fracture of both bones of the leg and (2) absence of involvement of any joint.

The treatment used consists, as mentioned, of the insertion of a  $\frac{1}{8}$  inch (0.3 cm.) steel pin through the upper end of the tibia on a level

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From the Department of Traumatic Surgery, Hurley Hospital.

portable x-ray apparatus; the roentgenogram is developed immediately and is interpreted before the fracture is fixed in plaster of paris. Fluoroscopic control is also recommended, to determine the proper alignment. Plaster of paris is then applied from the base of the toes to the middle third of the thigh, with the foot held at right angles midway



Fig. 2.—A typical tibiofibular fracture, at the time of the patient's admission to the hospital. It fulfils the indication for management with the double steel pin.

between eversion and inversion and with the knee in slight flexion. Pins are incorporated in the plaster of paris, their protruding ends being covered with corks and likewise incorporated in plaster of paris (fig. 3). A walking iron is then applied.



dressings is applied, incorporating both pins. The patient is kept in bed until his temperature is normal and there are no complications.

As to the etiology of fracture in this series of cases, 10 of the 23 fractures were caused by the patients' having been struck by an automobile; 5 were the result of accidents to persons riding in automobiles; 6 were due to falls, and 2 were the result of farm accidents.

In this series of cases, 10 fractures were compound and the remaining 13 were simple. The roentgenologic diagnosis of these 23 fractures classified 20 as comminuted fractures of the tibia and 3 as spiral fractures of the same bone. In each case the roentgenogram showed an accompanying fracture of the fibula, either at the same level or in the upper third. As to the location of the tibial fractures, 7 occurred at the junction of the upper and the middle third of the shaft, 5 at the junction of the lower and the middle third, 4 in the middle third, 3 in the lower third and 1 in the upper third. One tibia showed fractures at the upper and the middle third, 1 had 2 fractures involving the middle and the lower third, and another had 3 fractures in the upper half of the tibial shaft.

All but 4 of the patients were operated on within a period varying between two and five days after the occurrence of the accident. The operations for these 4 patients were necessarily delayed on account of other major injuries.

One of the outstanding features of this method of treatment is the materially shortened period which elapses before the patient is up and about after the operation (fig. 4). For 19 patients the average time spent in bed after the operation was six days. At the end of this time they were discharged on crutches. The number of days from operation to discharge varied from one to thirteen. The remaining 4 patients had to be kept in bed because of injuries other than the fractures. Many patients were discharged on crutches on the third day after the operation. When the operation took place on the day following admission and the patient was discharged on the third day after the operation, four days of hospitalization had been required, in contradistinction to the months spent in bed by patients given older methods of treatment. No patient whose condition was not complicated by other injuries had a total stay of more than seventeen days in the hospital.

On their discharge from the hospital on crutches, patients are instructed to return to the outpatient department at monthly intervals, unless discomfort or other symptoms bring them in sooner. At these periods check-up roentgenograms are taken to show the progress of the fracture.

In this series of cases the oldest patient was 66 years old and the youngest 7 years old. The fractures in patients from 20 to 40 years old

In the series there were 20 cases of sufficient duration to demonstrate functional union clinically and roentgenologically. The average length of time from the time of injury to the time of functional union was one hundred and fifty days, or one hundred and forty-three days

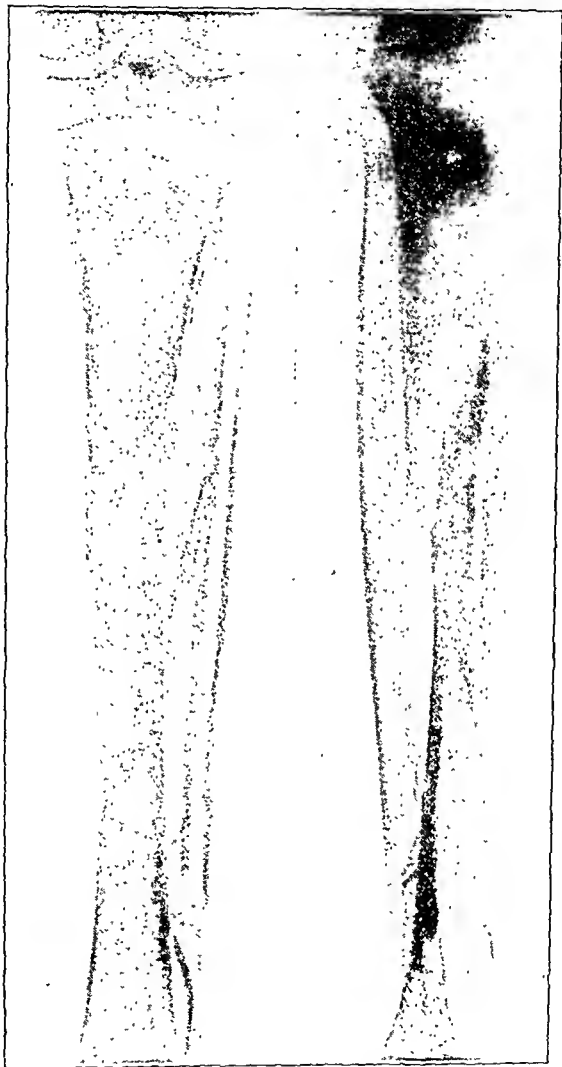


Fig. 5.—Tibiofibular fracture. Note that the pins have been removed and that union is satisfactory one hundred and sixteen days after the original injury. This fracture was kept in a plaster of paris dressing for an additional two months.

after insertion of the pins (fig. 5). However, the patient was kept in a cast and walking iron for an additional two months to insure firm union. The patients were free from all methods of immobilization at the end of an average period of seven months. Compound fractures

required on an average thirty-six days more to arrive at functional union. In only 1 case did any infection occur about the site of a pin. This was controlled by removal of the pin. There were no sequelae. In the 23 cases in which we have been able to follow the course through at least the first four months after the occurrence of the accident, there has been no instance of nonunion and but 1 instance of delayed union. The fracture in this single case was badly comminuted and compounded and was also infected originally. At present satisfactory union is slowly taking place. Satisfactory alinement and apposition were gained in each case. In no case was there slipping or angulation of the fragments following approximation with pin traction and immobilization by the original cast.

#### CONCLUSIONS

1. Fractures of the leg involving the tibia and the fibula together, not involving a joint, are best treated by the double steel pin traction in plaster of paris.

2. The compounding of a fracture is not an indication for a substitute method or for postponement of the use of this method, although a longer time is necessary for healing.

3. The period of hospitalization is minimal, and the patient is ambulatory early. The economic value of the treatment is obvious.

4. Satisfactory union may be expected within a period varying between seventy and ninety days.

5. The pins may be removed after about three and one-half or four months.

6. Functional union may be expected in five months, but we advise the continued use of the cast and the walking iron for an additional two months.

7. Nonunion has not occurred in this clinic with this type of management.

8. This method maintains anatomic approximation and insures a good functional result.

9. Satisfactory knee and ankle motion are noted after the removal of the cast.

10. The passive congestion associated with dependency of the leg and the irritation of the ends of the bones by the early use of graduated weight bearing are apparently definite stimuli to osteogenesis.

11. Patients are easily managed, happy and contented, and complain of very little pain or discomfort.

different modes of classification and terminology. Judd<sup>4</sup> found a substernal projection of the lobes of the thyroid in 50 per cent of patients presenting themselves for an operation on that gland, while the intrathoracic type was noted in less than 5 per cent. Goiter chiefly intrathoracic in location, without any cervical enlargement, was found in less than 1 per cent of the cases. Lahey<sup>5</sup> found no case of intrathoracic goiter in 4,363 cases of exophthalmic goiter or primary hyperthyroidism, but of 5,131 adenomatous goiters, 21 per cent extended into the superior mediastinum and the thorax. Of these goiters, 68 per cent reached nearly to the aortic arch, while 32 per cent extended to or below the arch. Sharer<sup>6</sup> found substernal goiter in 6 per cent of thyroidectomies and cited Higgins as stating that 10 per cent of goiters observed at operation were substernal and from 1 to 2 per cent intrathoracic. In 9,888 consecutive autopsies at the Cook County Hospital since 1929 there were found 1,222 nodular goiters. In this series only 3 true intrathoracic goiters were encountered, an incidence of 0.24 per cent.

Hemorrhage and cystic degeneration or other regressive changes are relatively common in substernal goiter, but suppuration is a rare complication. We are therefore reporting the following case of suppurative intrathoracic thyroiditis, the second case to be described in the literature.

#### REPORT OF CASE

*History.*—M. J., a Negress aged 27, entered the Cook County Hospital on Dec. 24, 1936. She was in such poor condition that a thorough history could not be obtained. However, it was learned that she had been generally well until eight days previously, when she noticed a pain in the right side of her chest, which continued, causing her to be short of breath. Cough was present since the onset, with expectoration, which at times was blood streaked. Chills were thought to have been present.

Physical examination revealed an obese Negress appearing acutely ill. The rectal temperature was 105 F., the pulse rate 154 and the respiratory rate 48. The essential findings were limited to the chest. There were dulness, bronchophony and tubular breathing in the lower lobe of the right lung and a friction rub over the right side of the chest. The heart showed no enlargement, and a systolic murmur was present over the apex. The abdomen was distended, and the liver was slightly enlarged and was tender. The diagnosis was lobar pneumonia of the lower lobe of the right lung.

The patient's condition improved gradually, the temperature falling by lysis. However, moderate lethargy remained, and in her fourth week in the hospital the oral temperature ranged between 99 and 101 F., the pulse rate between 100 and 120 and the respiratory rate between 20 and 30. The pulmonary symptoms were

4. Judd, E. S.: Intrathoracic Goiter, *Internat. Clin.* **1**:149, 1920.

5. Lahey, F. H., and Swinton, N. W.: Intrathoracic Goiter, *Surg., Gynec. & Obst.* **59**:627-637, 1934.

6. Sharer, R. F.: Substernal Thyroid, *Am. J. Surg.* **32**:56-62, 1936.

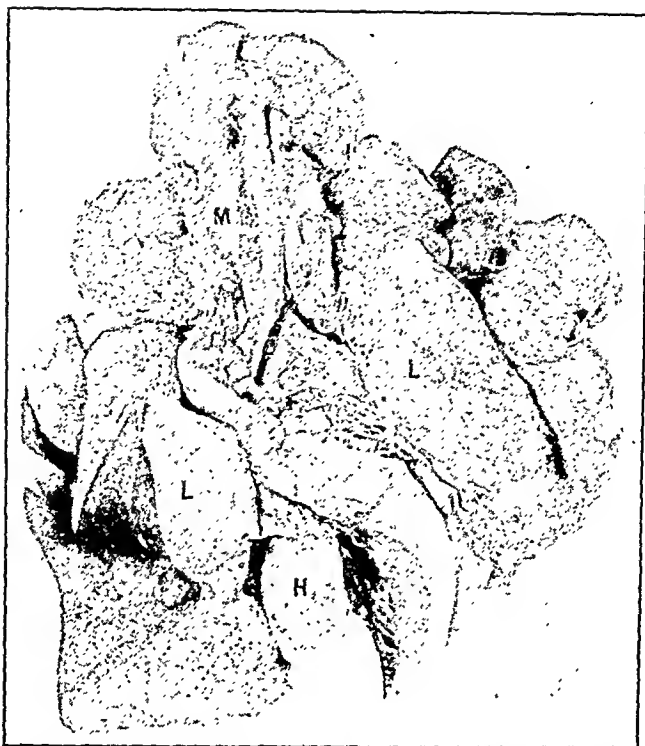


Fig. 2.—Anterior view showing nodular masses of the right lobe of the thyroid extending into the superior and anterior mediastinum and compressing the trachea. *L*, indicates lungs; *H*, heart.



Fig. 3.—Posterior view showing the nodose goiter in the posterior mediastinum (*M*) and its relation to the lungs (*L*) and the heart (*H*).

smaller ones were composed of small and medium-sized follicles filled with a pale-stained, often vacuolated colloid material and lined by a cuboid or low cylindric epithelium. In the larger nodes there were large follicles lined for the most part by a low cuboid epithelium. In places the structure was interrupted by dense accumulations of plasma cells and round cells which infiltrated the septums and extended also into the nodes. Mixed with the plasma cells were a moderate



Fig. 5.—Photomicrograph showing pneumococci in the wall of the abscess cavity. Gram-Weigert stain; magnification,  $\times 1,000$ .

number of iron-filled histiocytes. There were focal deposits of lime salts. In places, recent extravasations of blood were seen. In the periphery of the small nodes, accumulations of pus cells were present, but the most marked suppurative changes were encountered in the large nodes and seemed to select particularly those areas which were the sites of preceding regressive processes (fig. 4). In these areas the follicles were necrotic, the stroma was hyalinized and there were coarse calcium deposits as well as deposits from old and recent hemorrhages.

# POLYOSTOTIC FIBROUS DYSPLASIA

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My attention was recently drawn by Dr. Henry L. Jaffe, director of the laboratories at the Hospital for Joint Diseases, to a number of cases (4 from this and 4 more from other hospitals from which pathologic material was studied) presenting multiple osseous lesions and having sufficient features in common to differentiate them as a distinct clinical entity. The condition is designated as polyostotic fibrous dysplasia, for reasons to be indicated presently.

## DEFINITION AND NOMENCLATURE

The name "polyostotic fibrous dysplasia" is being used in the Hospital for Joint Diseases to designate a skeletal developmental anomaly affecting several or many bones with predominantly unilateral involvement. The involved bones show filling of their medullary cavities by gritty, grayish white fibrous tissue containing trabeculae of newly formed primitive bone. The condition apparently results from perverted activity of the specific bone-forming mesenchyme. It manifests itself in childhood or early adult life and evolves slowly, pursuing a protracted clinical course characterized by pain, deformity and a tendency to pathologic fracture of the affected bones.

A number of other cases which I regard as instances of the disease have been described in the literature under a bewildering variety of titles, such as, for instance, osteodystrophia fibrosa unilateralis, unilateral polyostotic osteitis fibrosa, unilateral Recklinghausen's disease, osteodystrophia fibrosa cystica generalisata limited to one side of the body, focal osteitis fibrosa, osteitis fibrosa in multiple foci, osteitis fibrosa with formation of hyaline cartilage and osteitis fibrosa disseminata.<sup>1</sup>

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From the Laboratory Division, Hospital for Joint Diseases.

1. A great deal of confusion exists with regard to the nomenclature of skeletal diseases, inherited largely from early investigators. The term "osteitis fibrosa" was employed in the German literature until comparatively recently to include the osseous lesions of hyperparathyroidism, Paget's disease, giant cell tumors, cysts of the bone and localized osteitis fibrosa. The term "fibrous osteodystrophy" has been applied to the same miscellaneous, pathologically unrelated group of osseous diseases, and in fact is still used in the *Index Medicus* synonymously with osteitis fibrosa. The terms nongeneralized fibrous osteodystrophy and unilateral fibrous osteodystrophy, introduced by some authors to obviate the confusion of the

(Footnote continued on next page)

The long duration of symptoms is an indication of the chronicity of the disease and the slow progression of its osseous lesions. The known duration of symptoms in my series of patients was more than twenty years on the average and in 1 instance as much as thirty-six years.

Precocious menstruation in children suffering from severe forms of the disease has been described by Goldhamer,<sup>2</sup> Borak and Doll<sup>3</sup> and recently by Albright and associates.<sup>4</sup> Goldhamer felt that this manifestation of *pubertas praecox* might in some way be attributed to involvement of the base of the skull. Its significance, however, remains a matter of conjecture.

The presence of hyperpigmentation of certain areas of the skin, apparently due to excessive melanin content, has also been mentioned by Goldhamer and particularly stressed by Albright and his associates as another feature occasionally found in association with the osseous lesions. The precise significance of hyperpigmentation in relation to the osseous lesions is impossible to decide in the present state of medical knowledge. In none of the cases which I have described was excessive pigmentation of the skin noted.

#### DISTRIBUTION OF OSSEOUS LESIONS

The osseous lesions tend to be exclusively or predominantly unilateral, apparently affecting either side without preference. However, bilateral lesions also occur, albeit in a minority of cases. In my material the lesions demonstrable on roentgen examination of the skeleton were entirely unilateral in 3 instances, predominantly unilateral in 2 and bilateral in 1. This is essentially in accord with the composite experience of other observers. The bones of the lower extremity, i. e., the femur and the tibia, according to my experience, are affected much more often than are the humerus and the radius. Combined involvement of lower and upper extremities is not infrequent.

The long bones of the extremities are most often affected and in the following order of frequency: femur, tibia, humerus and radius. Next in order of frequency are the bones of the skull (cranial vault

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2. Goldhamer, K.: *Osteodystrophia fibrosa unilateralis* (kombiniert mit *Pubertas praecox* und mit gleichseitigen osteosklerotischen Veränderungen der Schädelbasis), *Wien. klin. Wchnschr.* 47:218, 1934; *Fortschr. a. d. Geb. d. Röntgenstrahlen* 49:456, 1934.

3. Borak, J., and Doll, B.: *Halbseitige Recklinghausensche Knochenkrankheit mit Pubertas praecox*, *Wien. klin. Wchnschr.* 47:540, 1934.

4. Albright, F.; Butler, A. M.; Hampton, A. O., and Smith, P.: *Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction, with Precocious Puberty in Females*, *New England J. Med.* 216:727, 1937.



appearance probably reflects irregularities in the extent of erosion of the inner surface of the cortical bone (fig. 1).

*Chemical Findings in the Blood.*—Estimations of serum calcium were done in the laboratory in 5 cases in which the diagnosis of polyostotic fibrous dysplasia was confirmed by biopsy. The values ranged between 9.8 and 11.0 mg. per hundred cubic centimeters. Values for serum calcium ranging between 11.0 and 11.6 mg. have been noted by other observers also (Borak and Doll,<sup>3</sup> Albright and associates<sup>4</sup> and Freund and Meffert<sup>5</sup>). Apparently, then, the concentration of calcium in the serum may approach the upper limit of the normal range or even be slightly elevated.

Estimations of serum phosphorus show no significant deviation. Nor do any of the other chemical constituents of the blood, with the exception of phosphatase, show any appreciable alteration in their relative concentration.

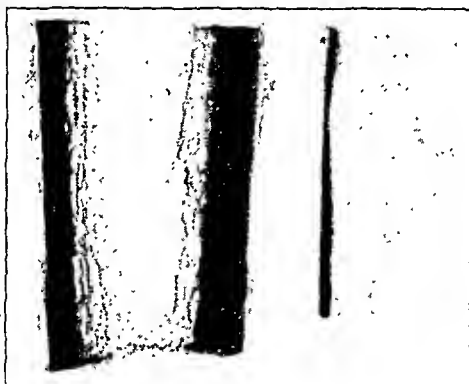


Fig. 1.—Roentgenogram of a portion of a diseased tibia (specimen taken for biopsy in case 2), illustrating the marked thinning of the cortex, the absence of deposition of periosteal bone, the endosteal erosion of the cortex and the filling of the medullary cavity by a homogeneous fibrous tissue containing tiny spicules of bone. Compare with the normal tibia from a woman, on the left.

The phosphatase content, however, was notably increased in 3 of my 4 cases, being 17, 18 and 22 units, respectively, when determined by Bodansky's method (as compared with the normal upper limit for adults of 4 units). Increased serum phosphatase has been noted by other observers also (Albright and associates<sup>4</sup> and Freund and Meffert<sup>5</sup>). The increased values for phosphatase in fibrous dysplasia afford additional support for the hypothesis of Bodansky and Jaffe<sup>6</sup> that the

5. Freund, E., and Meffert, C. B.: On the Different Forms of Non-Generalized Fibrous Osteodystrophy, *Surg., Gynec. & Obst.* 62:541, 1936.

6. Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: III. Serum Phosphatase in Diseases of the Bone; Interpretation and Significance, *Arch. Int. Med.* 54:88 (July) 1934.



Fig. 2.—*A*, roentgenogram of the right femur in case 1. *B*, roentgenogram of the lower third of the right femur and the upper end of the tibia in case 1.

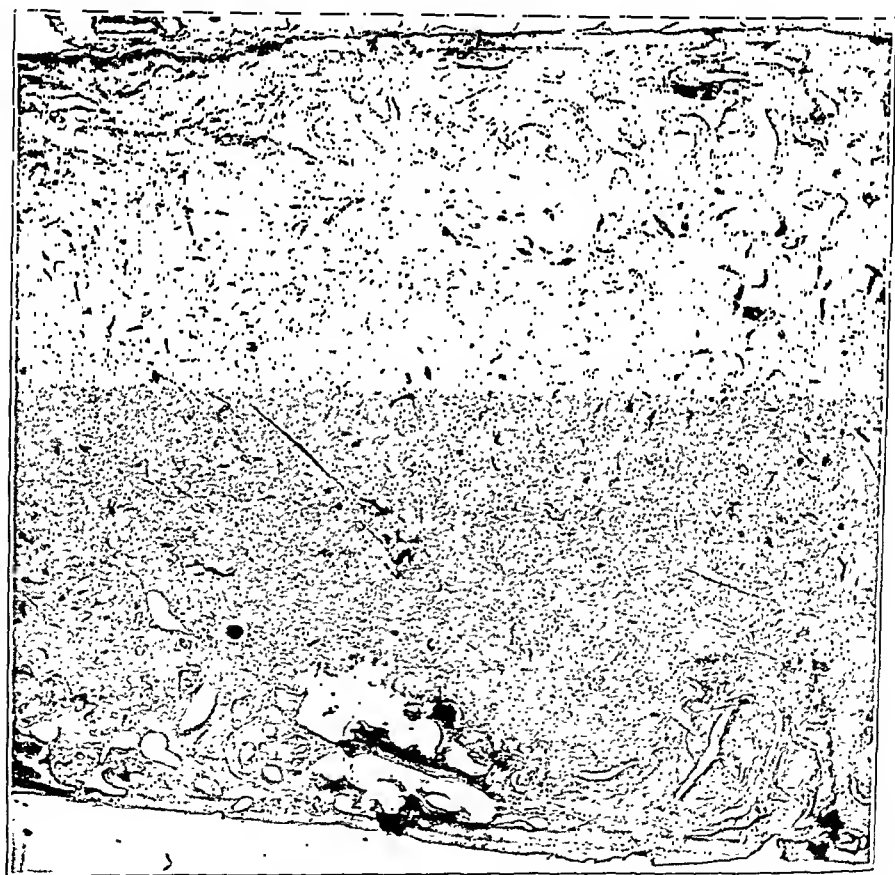


Fig. 3.—Biopsy specimen of a portion of the ninth rib in case 1, cross section, showing the absence of periosteal deposition of new bone, the thinning of the cortex with erosion of the endosteal surface and the medullary cavity filled solidly with fibrous tissue containing small spicules of calcified immature bone ( $\times 15$ ).



Fig. 7.—Roentgenogram of the skull in case 2. The arrows indicate the osseous defects.



Fig. 8.—Roentgenogram of the vertebral column and ribs in case 2, showing lesions in the seventh and eighth ribs.

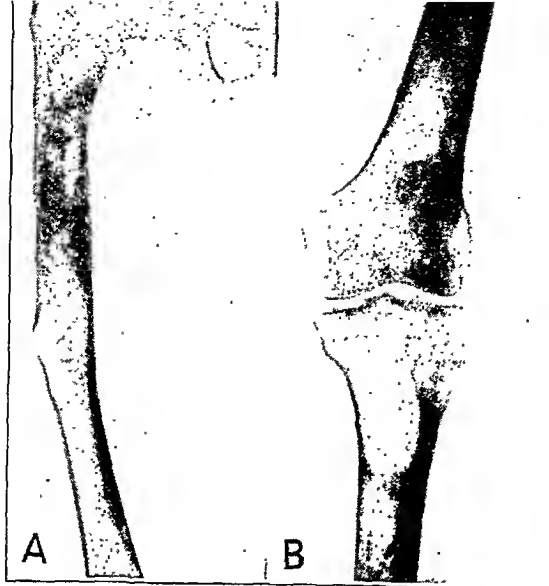


Fig. 2.—*A*, roentgenogram of the right femur in case 1. *B*, roentgenogram of the lower third of the right femur and the upper end of the tibia in case 1.

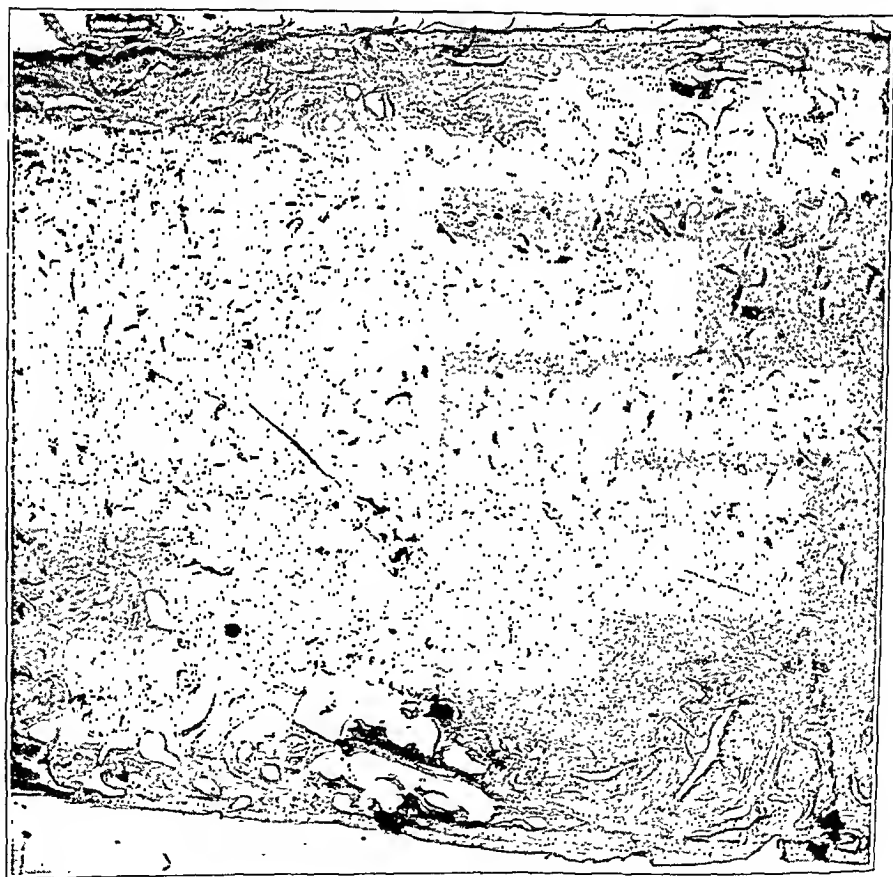


Fig. 3.—Biopsy specimen of a portion of the ninth rib in case 1, cross section, showing the absence of periosteal deposition of new bone, the thinning of the cortex with erosion of the endosteal surface and the medullary cavity filled solidly with fibrous tissue containing small spicules of calcified immature bone ( $\times 15$ ).

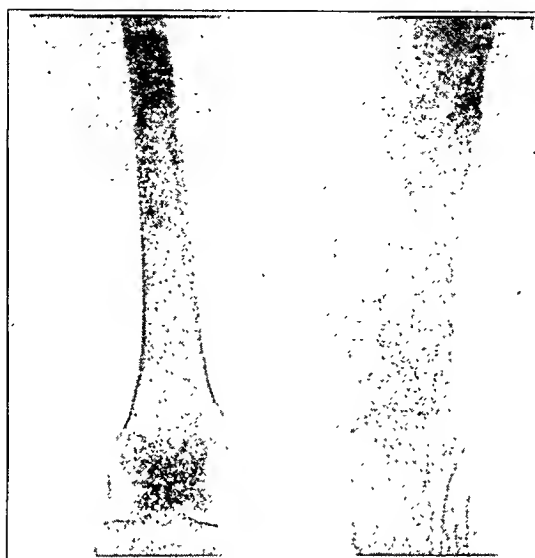


Fig. 5.—Roentgenogram of the lower third of the femurs and upper ends of tibias in case 2. Note the shortening of the affected extremity.

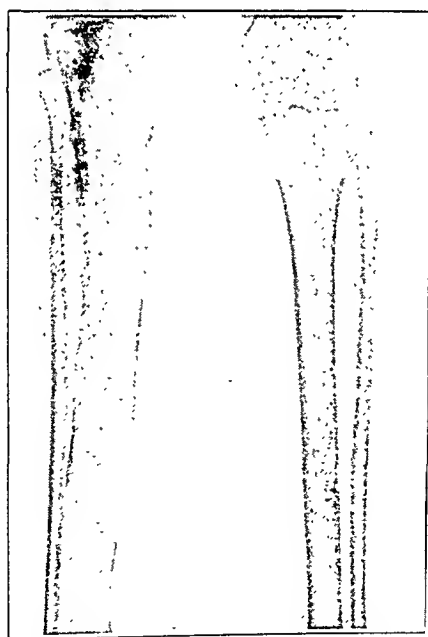


Fig. 6.—Roentgenogram of the tibias in case 2.



Fig. 9.—Biopsy specimen of the right tibia in case 2. Note the advanced lesion showing considerable deposition of fiber bone in the fibrous matrix and irregular focal calcification ( $\times 15$ ).



Fig. 10.—Biopsy specimen of the right tibia in case 2, cross section, showing absence of periosteal reaction, the thinning of the cortex with endosteal resorption and the replacement of the substantia spongiosa and filling of the medullary cavity by fibrous tissue containing irregular trabeculae of fibrous bone ( $\times 25$ ).



Fig. 11.—Roentgenogram of the pelvis and the upper portions of the femurs in case 3.

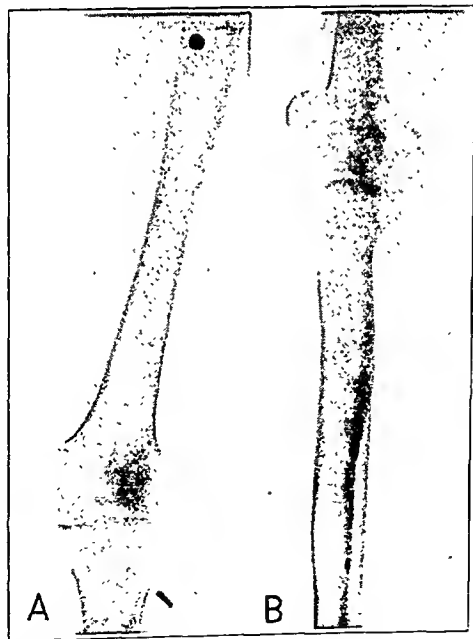


Fig. 12.—*A*, roentgenogram of the lower end of the left femur in case 3. *B*, roentgenogram of the left tibia in case 3.

fibrous tissue (fig. 15). Biopsy, in conjunction with the clinical and roentgenographic observations, indicated that this also was a case of polyostotic fibrous dysplasia.



Fig. 15.—Fibrous lesion in the left femur in case 3. *A*, islands of hyaline cartilage undergoing calcification, showing a few giant cells around the capillary extravasation ( $\times 15$ ). *B*, focal area of hyaline cartilage calcified at its periphery ( $\times 15$ ).

Convalescence following the operative procedure was uneventful, and the patient was discharged after three weeks. Several months later she was readmitted because of persistent pain, and a second curettage of the femur was performed. Biopsy



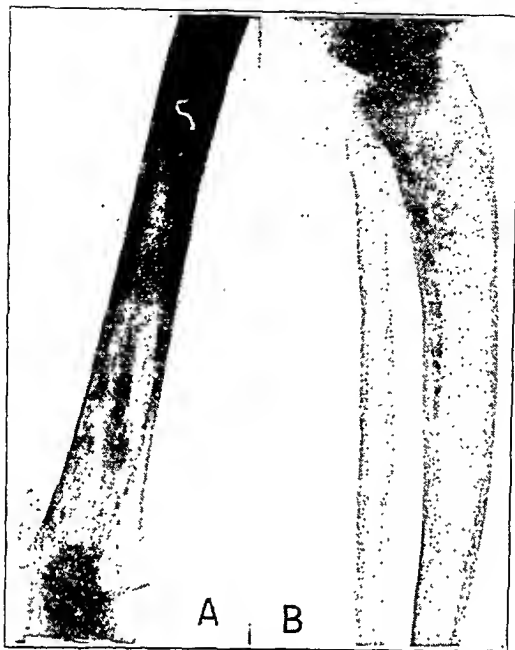


Fig. 16.—*A*, roentgenogram of the lower end of the right femur in case 4. *B*, roentgenogram of the right tibia in case 4.

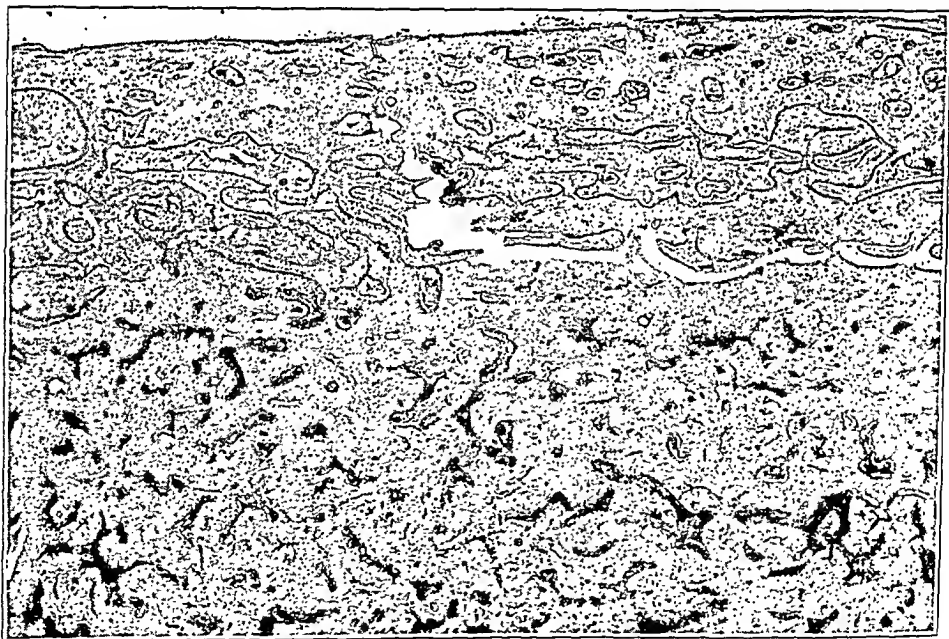


Fig. 17.—Biopsy specimen of the right tibia in case 4, longitudinal section, illustrating the absence of deposition of periosteal bone, the thinning of the cortex with erosion of the endosteal surface by fibrous tissue, which also replaces the substantia spongiosa and fills the medullary cavity and the deposition of trabeculae of primitive bone in the fibrous tissue ( $\times 15$ ).

avascular fibrous areas the trabeculae tend to be sparse in distribution; in the more vascular areas there is usually more extensive deposition of osteoid material and fiber bone (fig. 9). Some of the trabeculae show Howship's lacunas lodging osteoclasts, but on the whole there is comparatively little evidence of osteoclastic resorption. Deposition of calcium within the primitive new bone is variable in extent and distribution. Generally speaking, the bone is calcified poorly and in an imperfect, spotty fashion.

The basic fibrous tissue, on the whole, is relatively avascular, showing only occasional thin-walled vascular spaces. In some areas, however, it may be permeated by a moderate number of capillaries and even occasional small arterioles. Many of the blood vessels are in close proximity to the trabeculae of the bone. The latter are frequently surrounded by slender spaces which because of their endothelium-like lining suggest vascular spaces. Some capillaries appear empty, while others are congested and show small perivascular extravasations of blood. The presence of granules of hemosiderin within phagocytes indicates previous capillary hemorrhages which have been resorbed. In their vicinity one may also encounter small nests of giant cells, resembling osteoclasts. These multinuclear cells are basophilic and may have as many as ten or more nuclei; they are apparently formed by direct transformation and coalescence of the cells of the stroma. While some of the giant cells are distributed at the periphery of osseous trabeculae, thus suggesting an osteoclastic function, most of them are situated in the soft fibrous tissue. Sporadic islands of hyaline cartilage (fig. 15) may also occur within the fibrous tissue, although this is not constantly observed. The cartilage tends to become calcified, especially at its periphery. The significance of this feature will be discussed presently.

#### PATHOGENESIS

The characteristic pathologic feature of polyostotic fibrous dysplasia appears to be a disturbed function or development of the bone-forming mesenchyme, which results in replacement of the substantia spongiosa and filling of the medullary cavity of affected bones by fibrous tissue in which trabeculae of poorly calcified primitive new bone are developed by osseous metaplasia. The seemingly complex histologic picture becomes much easier to interpret if one predicates the multipotent character of this undifferentiated fibrous tissue, which normally gives rise to the substantia spongiosa and to the myeloid substances or fatty marrow but under pathologic conditions may develop in several anomalous ways. By osseous metaplasia, it gives rise to osteoid material and primitive fiber bone. By cartilaginous metaplasia, it gives rise to sporadic, isolated islands of hyaline cartilage, which tend to become calcified. By fibro-

entiated fibrous bone-forming mesenchyme, or initiates the disorder, remains of course a matter of conjecture. The clinical histories consistently describing symptoms dating back to early childhood strongly suggest a congenital basis for this curious anomaly of skeletal development. To my knowledge no instance of hereditary transmission of the disease has been recorded.

#### DIFFERENTIAL DIAGNOSIS

The common erroneous clinical diagnoses have for the most part already been indicated, the most frequent being that of hyperparathyroidism. Others include Recklinghausen's disease, unilateral Recklinghausen's disease, osteitis fibrosa cystica and "cystic disease." If only a single bone is examined roentgenographically, a mistaken diagnosis of giant cell tumor or of enchondroma may be made. In an occasional case unilateral involvement may even be mistaken for dyschondroplasia or Ollier's disease (skeletal enchondromatosis with a tendency to attack one side of the body). Traumatic coxa vara and juvenile osteomalacia also are diagnoses that may sometimes be made before further investigation reveals the real nature of the lesion. Paget's disease and malignant disease of the bone are two other possibilities which may sometimes be considered, but which can easily be dismissed after roentgenographic and pathologic examination.

*Hyperparathyroidism (Osteitis Fibrosa Cystica, Recklinghausen's Disease of the Bone).*—Hunter and Turnbull<sup>8</sup> (1931), who described in connection with their discussion of hyperparathyroidism 3 instances of the disease under the title "osteitis fibrosa in multiple foci," realized that the condition was not Recklinghausen's disease and warned against unnecessary exploration. Jaffe,<sup>9</sup> likewise, considering the condition in connection with the differential diagnosis of hyperparathyroidism, emphasized that it has frequently been misinterpreted as Recklinghausen's or Paget's disease. He also recognized that it constitutes a still unidentified entity, having a possible congenital basis. Nevertheless, even at present, polyostotic fibrous dysplasia is frequently confused with hyperparathyroidism. This difficulty arises principally from the fact that the osseous lesions in the two diseases may roentgenographically have a striking resemblance, which is readily misleading to those who are as yet unfamiliar with the clinical picture of polyostotic fibrous dysplasia. In at least 6 instances, as reported in the literature, patients

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8. Hunter, D., and Turnbull, H. M.: Hyperparathyroidism: Generalized Osteitis Fibrosa, *Brit. J. Surg.* **19**:203, 1931.

9. Jaffe, H. L.: Hyperparathyroidism (Recklinghausen's Disease of Bone), *Arch. Path.* **16**:63 (July): 236 (Aug.) 1933.

fibrous dysplasia, the basic histologic picture is one of fibrous tissue in which small trabeculae of immature fiber bone are deposited.

*Hand-Schüller-Christian Disease.*—Young subjects are particularly susceptible also to Hand-Schüller-Christian disease, and it too may cause punched-out rarefied lesions, visible roentgenographically in the skull and other bones. Even pathologic fracture of the femur may be simulated. The resemblance is superficial, however, so that xanthomatosis of the bones due to cholesterol can be ruled out usually on clinical grounds, because of the absence of the Christian syndrome, and if necessary by biopsy.

POSSIBLE RELATION TO LOCALIZED LESIONS APPARENTLY  
AFFECTING ONE BONE

The relation of localized fibrous osseous lesions apparently affecting only one bone to polyostotic fibrous dysplasia is a problem that cannot be definitely decided at present. Freund and Meffert<sup>5</sup> have described two such localized lesions apparently limited to the femur, which roentgenographically and also on biopsy closely resemble the polyostotic form of the disease. Recently I examined sections, sent to Dr. Jaffe, of a biopsy specimen obtained from a girl, aged 14, who presented a solid expanded lesion of the maxilla of the jaw. The condition was diagnosed clinically as central osteoma. The histologic appearance of the lesion, however, was indistinguishable from that seen in polyostotic fibrous dysplasia. Although there were no symptoms referable to other bones, roentgen examination of the skeleton, especially of the long bones, was recommended. Several similar cases have been described by Phemister and Grimson<sup>10</sup> as instances of fibrous osteoma of the jaw.

I have seen also a patient with a localized, expanded, rarefied lesion of the clavicle, diagnosed clinically as giant cell tumor or enchondroma. Biopsy showed the affected portion of the clavicle to be filled with whitish fibrous tissue such as is seen in polyostotic fibrous dysplasia. Roentgen examination of the other bones disclosed only a few suggestive lesions in the ribs.

Localized fibrous lesions of the type described may be regarded as representing a limited form of polyostotic fibrous dysplasia. Since the evolution of the disease is relatively slow, it would not be at all surprising to observe that other osseous defects subsequently develop in these patients. Another possibility is that there *are* multiple osseous lesions in these instances but that some of them are not sufficiently well developed to be visualized roentgenographically.

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10. Phemister, D. B., and Grimson, K. S.: Fibrous Osteoma of the Jaws, *Ann. Surg.* **105**:564, 1937.

ment, e. g., multiple exostosis and achondroplasia, no familial incidence or hereditary tendency has thus far been noted.

The long bones of the lower extremity (femur and tibia) are most frequently affected, but those of the upper extremity (humerus and radius) and also the skull, ribs, pelvis, phalanges and other bones may be involved. Epiphysoid bones (carpals and tarsals) and bones pre-formed in membrane as well as in cartilage may be affected. The epiphyses of affected bones as well as their metaphysial and diaphysial regions may be involved. The condition runs a slow, progressive clinical course over a period of many years, even decades, with a tendency to spontaneous fracture and deformity of affected bones. The characteristic pathologic feature appears to be a disturbed function or development of the bone-forming mesenchyme, resulting in the filling of the medullary cavity of affected bones by fibrous tissue, in which spicules of poorly calcified primitive fiber bone are developed by osseous metaplasia. Some areas, however, may show a predominantly collagenous differentiation with comparatively little deposition of new bone. Furthermore, small islands of hyaline cartilage (remote from the epiphysial plate) may also be formed by chondrogenic metaplasia.

The aforementioned changes result in prominent widening of affected bones, marked thinning of their cortices and replacement of the cancellous bone and bone marrow by a fibrous, whitish, gritty, solid tissue. The bones on roentgen examination cast a shadow of diminished density, suggesting a rarefied or porotic trabeculated lesion, replacing bone and usually interpreted as indicating cystic disease. Thus, the condition with which polyostotic fibrous dysplasia is most often confused is *ostitis fibrosa cystica* (Recklinghausen's disease of bone). The not infrequent observation of increased values for calcium and phosphatase in the serum in cases of fibrous dysplasia affords another pitfall, suggesting the erroneous diagnosis of hyperparathyroidism. Indeed many patients suffering from polyostotic fibrous dysplasia are subjected to exploration of the neck for parathyroid adenoma only to have the surgeon find normal parathyroid glands. The differentiation from other skeletal diseases has been discussed.

## METASTATIC CARCINOMA

Metastatic carcinoma was by far the most frequent neoplastic lesion of this series. Of 291 spinal tumors, 172 (59.1 per cent) were metastatic carcinomas. Schlesinger<sup>1</sup> and Frazier,<sup>2</sup> the former obtaining his data from autopsies and the latter taking his from operations, pointed out the marked frequency of metastatic lesions of the spine. In adults such lesions must be considered in the differential diagnosis of any tumor affecting the vertebral column. Table 1 lists the sites of origin of the 172 tumors.

Schlesinger in 13,500 autopsies found 59 metastatic carcinomas of the spine and listed their sites of origin (table 2).

These two tables present notable differences. Prostatic carcinoma is probably not as frequent as is indicated by the figures in table 1, since in obtaining these figures all the patients with prostatic cancer in the Brady Urological Institute of the Johns Hopkins Hospital were

TABLE 1.—*Site of Origin of Metastatic Carcinomas of the Spine Observed in the Laboratory of Surgical Pathology*

Site of Origin	Number of Cases
Prostate.....	86
Breast.....	60
.....	14
.....	5
.....	4
Thyroid.....	1
Lung.....	1
Nasopharynx.....	1
Total.....	172

examined. It will also be noted that cancer of the female genital tract is not listed in table 1. Behney<sup>3</sup> has shown that of 55 carcinomas of the uterine cervix which metastasized, 5 had metastases to the lower lumbar vertebrae. This should make the condition a frequent source of metastasis to the spine. These and other discrepancies in the two tables are explained by the different methods by which the material was collected. Table 2 undoubtedly shows more nearly the correct incidence.

Carcinoma of the breast may be considered the most frequent cause of metastases to the vertebrae. In a series of 100 carcinomas of the breast metastasizing to bone (Geschickter and Copeland<sup>4</sup>) 60 of the

1. Schlesinger, H.: Beiträge zur Klinik der Rückenmarks- und Wirbeltumoren, Jena, G. Fischer, 1898.

2. Frazier, C. H., and Allen, A. R.: Surgery of the Spine and Spinal Cord, New York, D. Appleton and Company, 1918.

3. Behney, C. A.: Advanced Carcinoma of the Cervix, with a Report of One Hundred and Sixty-Six Necropsies, Am. J. Obst. & Gynec. 26:608, 1933.

4. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, ed. 2, New York, American Journal of Cancer, 1936.

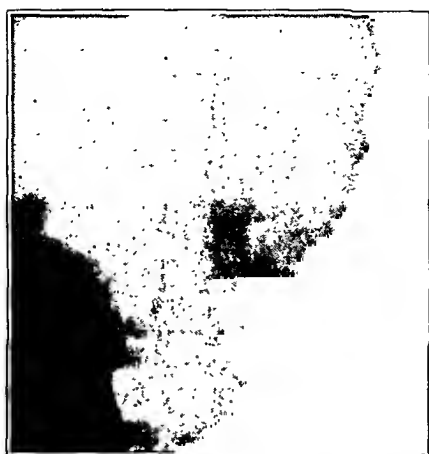


Fig. 1 (case 1).—Metastatic carcinoma of the breast in the fourth lumbar vertebra. The roentgenogram shows osteosclerosis following irradiation. (Case of Dr. Warner Watkins, Phoenix, Ariz.)



Fig. 2 (case 2).—Metastatic lesion of carcinoma of the prostate in the spine. The roentgenogram shows sclerosis of the body of the second lumbar vertebra.

encountered. As regards the roentgenologic picture, the tendency of metastatic carcinoma of the prostate to cause osteosclerosis is the only consistently recognizable feature. Roentgen irradiation of the affected area, rest and sometimes operative relief of compression of the spinal cord are indicated. The affected part of the spine should be protected by immobilization or by hyperextension. Life is often greatly prolonged by roentgen therapy, and pain may be controlled.

#### TUMORS OF GENERALIZED DISTRIBUTION

It is well to consider generalized neoplastic diseases in conjunction with metastatic carcinoma, since multiple myeloma, the most important representative of this group, as regards the spine, is easily confused with metastatic carcinoma.

Among 30 cases of multiple myeloma in the surgical pathologic laboratory there were 14 with leading symptoms involving the spine. Multiple myeloma is a tumor of adult life, the period of its greatest incidence being the sixth decade. The pain in 70 per cent of all cases (Geschickter and Copeland) begins in the lumbar and in the sacral region. In 40 per cent of cases compression of the spinal cord develops. These considerations justify the inclusion of multiple myeloma in a group of tumors affecting the spinal column.

The roentgenogram is often diagnostic. The lesions are rarefied punched-out areas and commonly produce pathologic fracture. They are multiple or become multiple in more than 95 per cent of cases. At times the punched-out areas may be seen in the vertebrae, but more often there is a pathologic fracture (fig. 4). Sacral lesions show the characteristic defects in the roentgenogram.

Because of the age at which its onset occurs and the multiplicity of its lesions, multiple myeloma is difficult to distinguish from metastatic carcinoma. Both, of course, are hopeless conditions, and the differential diagnosis is sometimes of academic interest only. The following points are useful: Metastatic carcinoma is by far the more common. The roentgen picture of multiple myeloma is the more distinctive. The fact that Bence Jones bodies are present in the urine is in favor of a diagnosis of multiple myeloma, and their absence would suggest a diagnosis of metastatic carcinoma, though they may or may not be present with either condition. The presence of chronic nephritis, with nitrogen retention and high serum proteins, is definitely favorable to a diagnosis of multiple myeloma. Biopsy is the last resort. Roentgen therapy is the treatment of choice for both conditions. The lesions of multiple myeloma respond more rapidly than do those of metastatic carcinoma.

Hodgkin's granuloma, lymphosarcoma, myeloid tumors and the xanthomatous lesions were found to be rare or absent in our series of



are most often affected. When a vertebral body is involved, collapse of that body occurs. We had 1 such case. Anspach<sup>8</sup> reported a case, the patient being a 5 year old boy, in which the body of the tenth thoracic vertebra was involved. Triangular collapse of this body occurred, but with clearcut edges, which distinguished the condition from tuberculosis. With irradiation the lesions of the bone heal in most instances.

#### BENIGN PRIMARY TUMORS OF THE VERTEBRAL COLUMN

The second largest group of spinal tumors is composed of primary tumors of the vertebral column, which numbered 58 in this series. The relative frequency of the various tumors is listed in table 3.

In all there were 37 benign lesions and 21 malignant lesions affecting the spinal column. Among benign tumors the most common are giant

TABLE 3.—*Primary Tumors of the Vertebral Column*

Types of Tumor		Number of Cases
Benign		
Giant cell tumor.....		15
Osteochondroma.....		10
Bone cysts.....		7
Chondroma.....		3
Hemangioma.....		2
Malignant		
Osteogenic sarcoma		
Chondrosarcoma.....		8
Osteolytic sarcoma.....		4
Sclerosing sarcoma.....		4
Chordoma.....		5
Benign.....		37
Malignant.....		21
Total.....		58

cell tumor (in which type benign bone cysts may be included) and osteochondroma. This corresponds to the relative incidence of these tumors in the rest of the skeleton.

*Giant Cell Tumors.*—There were 15 giant cell tumors in the present series. In 1935 Murphy<sup>9</sup> collected 45 from the literature and pointed out that the typical history is characterized by injury to the spine in a young adult, followed by pain, tumor and occasionally kyphosis. Symptoms of pressure on the spinal cord may develop. The age incidence in our series is in accord with the findings of Murphy. Most of the patients were young adults. One girl, however, was 7 years of age and one man 62. The incidence of the condition in the male sex exceeded its incidence in the female sex in the proportion of 9 to 5.

8. Anspach, W. E.: Xanthomatosis with Involvement of a Vertebral Body, *Am. J. Dis. Child.* 48:346 (Aug.) 1934.

9. Murphy, G. W.: Giant Cell Tumor of the Spine, *Am. J. Roentgenol.* 34: 386, 1935.

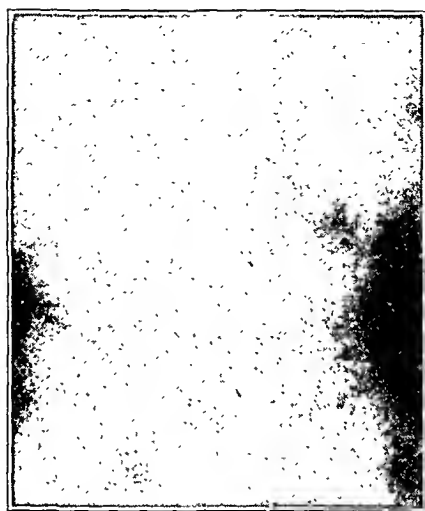


Fig. 5.—Giant cell tumor of the spine. The roentgenogram shows an extensive process of rarefaction, involving chiefly the third and fourth lumbar vertebrae. The fourth lumbar vertebra is almost entirely destroyed. The third lumbar vertebra shows only as a poorly defined shadow. A portion of the neural arch of the second lumbar vertebra is also destroyed. (Case of Dr. B. S. Putts, Erie, Pa.)

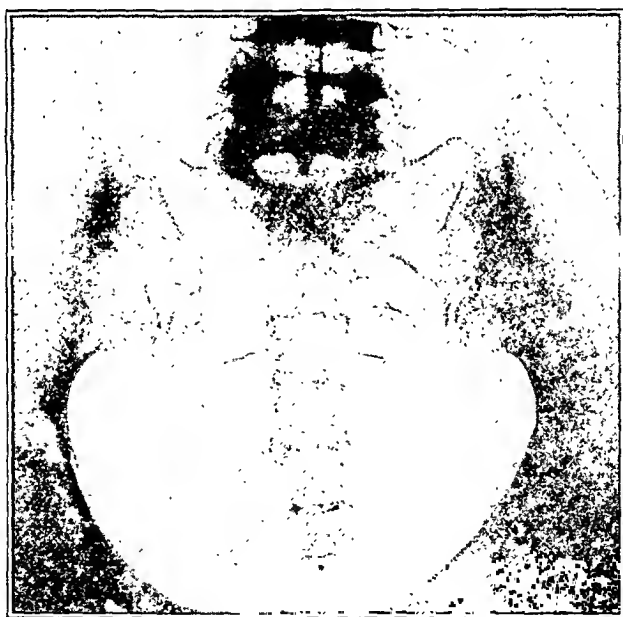


Fig. 6.—Giant cell tumor of the sacrum. The roentgenogram shows a rarefied area in the upper right half of the sacrum. The margins are clearcut, and faint trabeculations are visible. (Case of Dr. G. E. Bennett, Baltimore.)

Giant cell tumor may be diagnosed from the roentgenograms and treated with roentgen irradiation. In some cases operative procedures are necessary in order to relieve compression of the spinal cord or to stabilize the spinal column and prevent compression. An "aspiration biopsy" can be done and is not contraindicated in doubtful cases.

*Bone Cysts.*—In view of the relative frequency of giant cell tumor of the spine, one would expect bone cysts to be more common in this location. This, however, is not the fact. Multiple involvement of the spine, with bone atrophy and cyst formation, occurs as part of the syndrome of generalized osteitis fibrosa. There were 5 instances of such lesions. In 2 of these cystic lesions of the spine complicated the generalized skeletal deformity. In both of these cases pain in the back of increasing severity, was followed by signs of compression of the spinal cord. The roentgenologic picture showed diffuse atrophy of bone, bending deformities of the spine (most commonly kyphosis and scoliosis) and rarefaction and expansion of the bodies of one or more vertebrae or of a portion of the neural arch. In 3 other cases of generalized osteitis fibrosa demineralization and bending deformity of the spine were not accompanied by formation of the cysts.

No histologically verified solitary bone cysts of the spine, such as are commonly found in the shaft of the long bones in children, were recorded in this series. There was 1 such cyst occurring at the sacroiliac joint. In another instance a patient had been previously operated on for benign giant cell tumor, and at a second operation a similar lesion which had undergone cystic change was found above the original site. Microscopically this appeared to be a giant cell variant of the bone cyst. The absence of typical bone cysts in association with tumors of the spinal column lends support to the opinion that the usual bone cyst of the long bones is a benign giant cell tumor which has undergone healing. The failure of such a healing reaction to follow giant cell tumors of the vertebrae is explained by the cancellous structure of the vertebrae and by the absence of a well defined cortex of compact bone. The less rapidly growing giant cell tumors may take on a histologic character which justifies their classification as giant cell variants of the bone cyst, but active giant cell tumor tissue is rarely absent.

*Osteochondroma.*—Benign exostoses, which are so common in the remainder of the skeleton, are next in frequency. There were 10 of these in this series. Two were multiple exostoses affecting the remainder of the skeleton as well; the other 8 were all solitary lesions. With 2 exceptions the tumors arose from the neural arch or from one of its processes. In 3 cases the tumor projected into the spinal canal and gave rise to the symptoms of compression of the spinal cord. Case 4 is an instance of intraspinal osteochondroma.

*Chondroma*.—Camp, Adson and Shugrue<sup>12</sup> stated that chondroma of the spinal column is rare. In this series there was but 1 chondroma which was examined microscopically (case 5).

CASE 5.—A white man aged 23 complained of pain in the lower part of the back, difficult urination and constipation, present for four months. Rectal examination disclosed a mass anterior to the sacrum. Roentgen examination (film not available) four months after the onset was reported as showing a "diffuse shadow" in the sacral region. Seven months after the onset a colostomy was performed for intestinal obstruction. The patient died four and one-half years after the onset, and postmortem examination revealed a large, smooth encapsulated tumor arising from the sacrum and projecting into the pelvis but not obstructing the intestine. The microscopic diagnosis was chondroma.

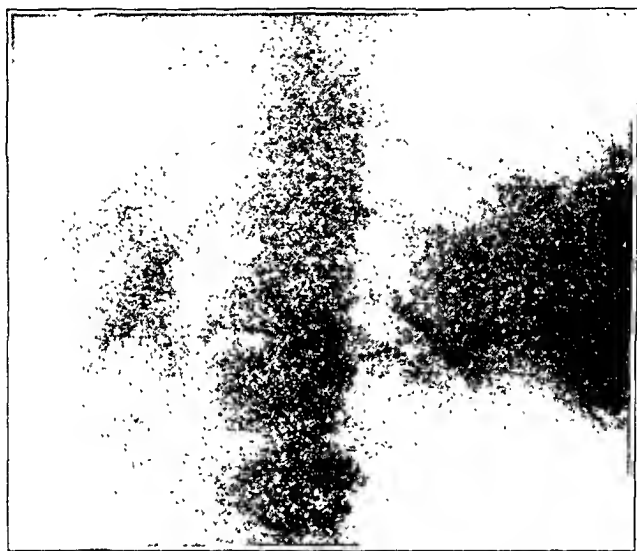


Fig. 10.—Osteochondroma involving a transverse process of the first lumbar vertebra. The tumor is well circumscribed and contains fine trabeculations. (Bone Registry American College of Surgeons no. 21.)

We cannot be sure of the diagnosis. No sections are available, and it is well known that chondrosarcoma and chordoma may be mistaken for chondroma. Examination of 2 other patients with tumors which are included in this group showed large rarefied areas in the sacrum, with cleancut margins. In neither case was the diagnosis proved by microscopic examination, and it may well be that the growths were giant cell tumors and not chondromas. Their slight response to irradiation

12. Camp, J. D.; Adson, A. W., and Shugrue, J. J.: Roentgenographic Findings Associated with Tumors of the Spinal Column, Spinal Cord, and Associated Tissues, *Am. J. Cancer* 17:348, 1933.

*Hemangioma.*—Bucy and Capp<sup>13</sup> have contributed an excellent article on primary hemangioma of bone. They pointed out that when the vertebral bodies are involved vertical striations are produced which form an easily recognized roentgenologic picture (fig. 13). When a hemangioma involves a flat bone, such as the sacrum, a marked sunray effect is produced in the periosteal zone. This periosteal reaction is so marked and so regular that it may be distinguished from the somewhat similar picture of sclerosing osteogenic sarcoma in the same region. They also stated that the affected bone does not collapse and produce pain but that the first symptoms are those of compression of the spinal



Fig. 13 (Bone Registry American College of Surgeons no. 940).—Multiple hemangioma of the vertebral bodies. The roentgenogram shows vertical striations in the bodies of the third, the fifth and the sixth thoracic vertebrae. (Courtesy of Dr. P. C. Bucy and Dr. C. S. Capp.)

cord. The histories of the 2 hemangiomas in our series support this statement. One tumor affected the laminae; the other, the transverse process. The latter case is reported below.

CASE 6.—A white man aged 55 suffered pain in the left thigh for two and one-half years and loss of control of the bladder for three and one-half months. Saddle anesthesia and hyperactive reflexes were present. The Queckenstedt test

13. Bucy, P. C., and Capp, C. S.: Primary Hemangioma of Bone with Special Reference to Roentgenologic Diagnosis, *Am. J. Roentgenol.* **23**:1, 1930.

of pressure on the spinal cord, in 1 these symptoms preceded the pain in the back. Detailed histories were not available in the 2 remaining cases. In 5 cases death occurred from three months to three years after the onset. One patient is living seven years after the onset. The tumor is growing slowly at the present time. Two patients have not been traced. The tumors occurred in all portions of the spine. Cases 7, 8 and 9 illustrate the varying types of chondrosarcoma.

*CASE 7.—Single primary lesion.*

A white man aged 35 complained of pain in the back following an injury in May 1935. Roentgen examination of the spine in September revealed no abnormality, but further examination in December showed partial destruction of the body of the ninth thoracic vertebra with a faint paravertebral fusiform shadow



Fig. 14 (case 7).—Primary chondrosarcoma of a thoracic vertebra. The roentgenogram shows destruction of the body of the ninth thoracic vertebra without any appreciable collapse. A faint paravertebral fusiform shadow is visible. (Case of Commander H. E. Ragle [MC], U. S. Navy, Washington, D. C.)

(fig. 14). Spastic paralysis of the lower extremities developed in February 1936. In March a hemathorax was discovered, and tubercle bacilli were found in the sputum. Tuberculosis of the spine was considered the probable diagnosis. A roentgen examination at this time revealed an increase in the paravertebral shadow. The patient died in November, and at postmortem examination the region extending from the eighth thoracic vertebra to the tenth was found to be the site of a chondrosarcoma which had destroyed the spine and the spinal cord and had metastasized to the lungs.

*CASE 8.—Multiple primary lesions.*

A white girl aged 14 complained of difficulty in walking present nine months and of pain in the back and inability to flex the muscles of the neck present for one month. This condition progressed to a flaccid paralysis of both lower extremi-



Fig. 16.—Primary chondrosarcoma of the spine with multiple lesions. The photograph of the spine at autopsy shows multiple cartilaginous nodules in the paravertebral region of the thoracic spine.



Fig. 17 (case 9).—Chondrosarcoma of the spine secondary to benign exostoses. The roentgenogram shows a faint paravertebral mass lateral to the third, fourth and fifth lumbar vertebrae. Irregular dense areas are visible within the tumor.

tumors is from 20 to 40 years. He also stated that the average duration of life for these patients is twenty-eight and a half months, the extremes of age being 4 months and 18 years.



Fig. 18.—Osteogenic sarcoma (sclerosing type) involving the sacrum and the adjacent ilium. The roentgenogram shows a sclerosing process which extends out into the soft parts in the form of radiating bony spicules.

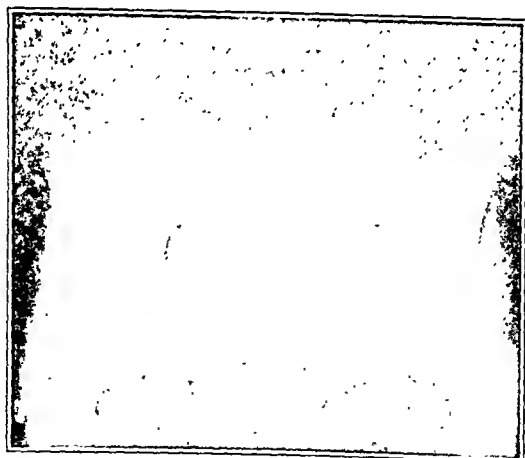


Fig. 19.—Osteolytic osteogenic sarcoma of the sacrum. The roentgenogram shows rarefaction in the upper part of the sacrum, with irregular margins.

In the laboratory of surgical pathology there are records of 5 cases of chordoma. In 3 of these the tumor was sacrococcygeal, in 1 occipital and in the other cervical. The ages of the patients ranged from



growths metastasize. There were metastases from 2 tumors in our series, to the regional lymph nodes in 1 instance and to distant soft tissues in the other.

The microscopic picture is variable. Alezais and Peyron.<sup>17</sup> basing their studies on the histogenesis of the notochord in the embryo, distinguished three general types. The first and most primitive type of chordoma, according to their studies, should correspond to that stage in which the notochord is evaginated from the entoderm. They could, however, find no tumor corresponding to this stage. A second and more clearly differentiated type of chordoma would be formed by solid cords of polyhedral and globular cells with abundant granular cytoplasm. Some of the cells show vacuolation. In our series 3 chordomas



Fig. 21.—Chordoma of the sacrum. The roentgenogram shows destruction of the lower portion of the sacrum, with a large intrapelvic mass (from previously published case, Harnos, O., and Palmer, L. A.: *Chordomata and Report of a Case*, *Virginia M. Monthly* 62:638 [Feb.] 1936).

were of this type (figs. 22 and 23). In the third stage these cells become increasingly vacuolated and a homogeneous intercellular mucinous matrix is produced. Two of the tumors in our series presented a microscopic picture corresponding to that of this adult type of chordoma (fig. 24).

Irradiation seems to have little effect on this type of tumor. Surgical excision may be attempted, but recurrence is the rule.

17. Alezais and Peyron: *Sur l'histogénèse et l'origine des chordomes*, *Compt. rend. Acad. d. sc.* 174:419, 1922.

Hospital, there were 6 which affected bone and which on microscopic examination were found to be sympathicoblastomas. Records of 6 additional tumors of this type were found in the files of the laboratory of

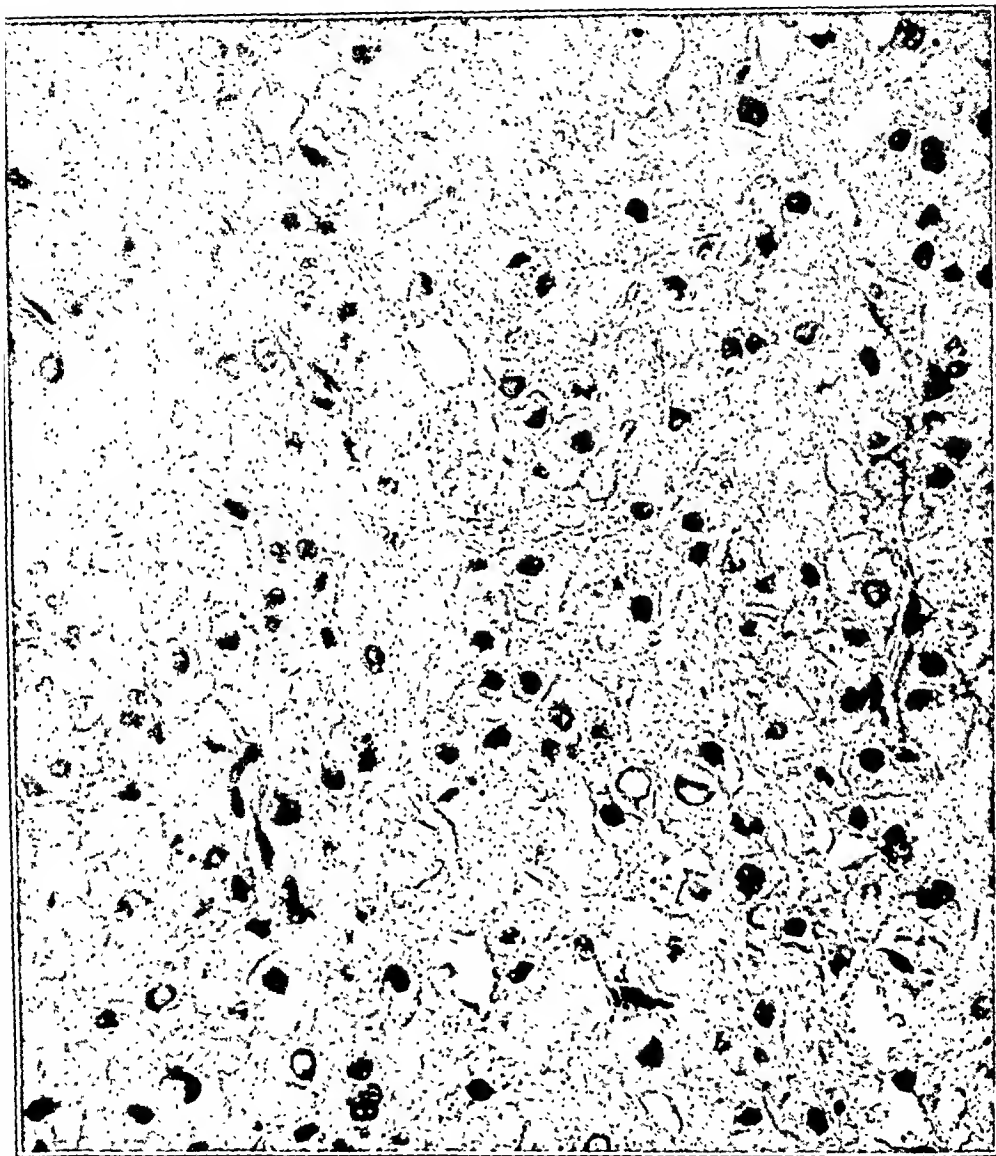


Fig. 23.—High power photomicrograph of chordoma cells in the stage of vacuolization. (Case of Dr. W. S. Hastings, Fox Chase, Philadelphia.)

surgical pathology. These 12 tumors were types of sympathicoblastoma in all stages of differentiation. Summaries of the clinical histories of the cases are given at the end of the section describing the tumors.

high, since sympathicoblastoma is generally a tumor of childhood and one of the commonest malignant tumors of that period. Scott and Palmer,<sup>18</sup> however, collected 32 cases of neuroblastoma arising from the sympathetic nervous system outside the adrenal medulla and found that the ages of the patients ranged from 1 month to 64 years. Schultz<sup>19</sup> tabulated 58 cases of benign ganglioneuroma and found that 26 of the tumors occurred in adults and 22 in children. The ages of 10 of the patients were not stated. Less clearly differentiated forms of neuroblastic tumor may also occur in adults (Wright;<sup>20</sup> Symmers;<sup>21</sup> Barnewitz;<sup>22</sup> Capaldi;<sup>23</sup> Busch;<sup>24</sup> Blumensaat<sup>25</sup>).

Both Schultz and Scott found the tumors more common among female than among male patients. In our series the incidence was equal in the two sexes.

The clinical histories in these cases were fairly uniform. The complaints were those of pain in the back, pain at the nerve roots or symptoms of compression of the spinal cord. Four patients showed symptoms of pressure on the spinal cord. In 6 others pain in the back preceded the onset of compression of the spinal cord. The remaining 2 had pain in the back as the only complaint. Pain at the nerve roots was an additional complaint of 5 patients. One expects, then, a tumor which destroys bone and presses on the spinal cord or on the nerve roots. Such is the case, as is seen by an examination of the roentgenologic, operative and postmortem evidence.

The roentgenogram showed a purely destructive lesion in 7 cases. In only 1 case was there a purely osteosclerotic lesion. In 3 cases osteolysis and osteosclerosis were both present. In addition, a paravertebral mass was visible in 4 of the roentgenograms. Figure 25 presents an example of osteosclerosis of the body of the tenth thoracic vertebra. In figure 26 a mass surrounded by a fairly well formed osseous

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18. Scott, E., and Palmer, D. M.: Intrathoracic Sympathicoblastoma: Report of a Case, *Am. J. Cancer* **16**:903, 1932.

19. Schultz, O. T.: Tumors of Neurogenous Origin, in Abt, I. A.: *Pediatrics*, Philadelphia, W. B. Saunders Company, 1926, vol. 8, p. 744.

20. Wright, J. H.: Neurocytoma or Neuroblastoma, a Kind of Tumor Not Frequently Recognized, *J. Exper. Med.* **12**:556, 1910.

21. Symmers, D.: A Recurrent Neuroblastoma of the Scapular Region, *J. A. M. A.* **60**:337 (Feb. 1) 1913.

22. Barnewitz: Zur Kenntnis des Neuroblastoma sympathicum, *Frankfurt. Ztschr. f. Path.* **26**:317, 1921.

23. Capaldi, B.: Zwei Fälle von Sympathikoblastom, *Frankfurt. Ztschr. f. Path.* **35**:83, 1927.

24. Busch, E.: On Ganglioneuroblastoma Sympathicum, *Acta path. et microbiol. Scandinav.* **5**:289, 1928.

25. Blumensaat, C.: Zur Kenntnis der Neuroblastome des Sympathicus beim Erwachsenen, *Virchows Arch. f. path. Anat.* **269**:431, 1928.

shell is visible. This view also shows destruction of the left transverse process and pedicle of the third lumbar vertebra. Figure 27 is a roentgenogram of a postmortem specimen. The tumor stimulated reactive bone, thus producing the radiopaque area seen in the region of the spinal canal. These osteosclerotic changes may take place in the substance of the bone or may occur as a periosteal reaction.

The sympathicoblastomas in this series occurred in the thoracic or lumbar portion of the spine, with the exception of the tumor in case 10, which involved both the cervical and the thoracic region. Autopsy was

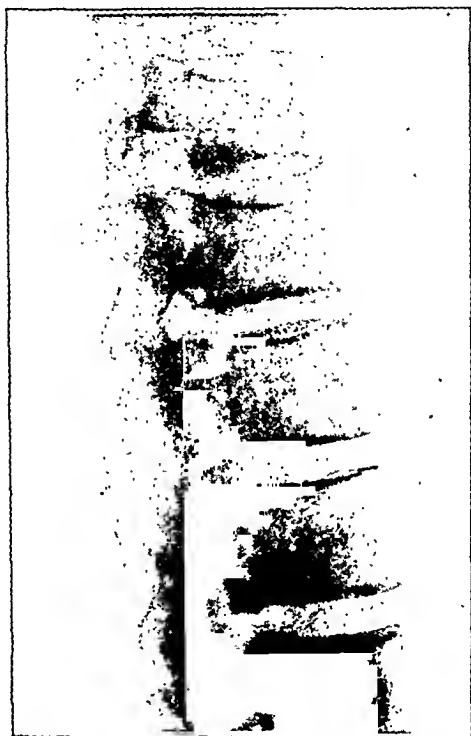


Fig. 27 (case 14).—Gangliosymphaticoblastoma. The roentgenogram was taken of the postmortem specimen. It shows an osteosclerotic lesion in the region of the neural arch and spinal canal.

performed in only 50 per cent of the cases, but from correlation of the roentgenologic and the operative findings it is evident that there was a paravertebral mass (fig. 32) lying on the bodies of the vertebrae in 10 cases. One of the 10 tumors was a metastasis from the adrenal gland (case 15), but since it acted like a paravertebral tumor we have included it in this series. Of the 2 remaining tumors, 1 was intradural (case 18) and the other extradural (case 17). This intraspinal location is of frequent occurrence, since all the neuroblastic cells must migrate

rise to neuroblasts and glial cells. The neuroblasts of the sympathetic nervous system form sympathogonia. These are small cells with a round or oval hyperchromatic nucleus, scanty cytoplasm and at times delicate fibrils. As differentiation proceeds, the nuclei become larger and more

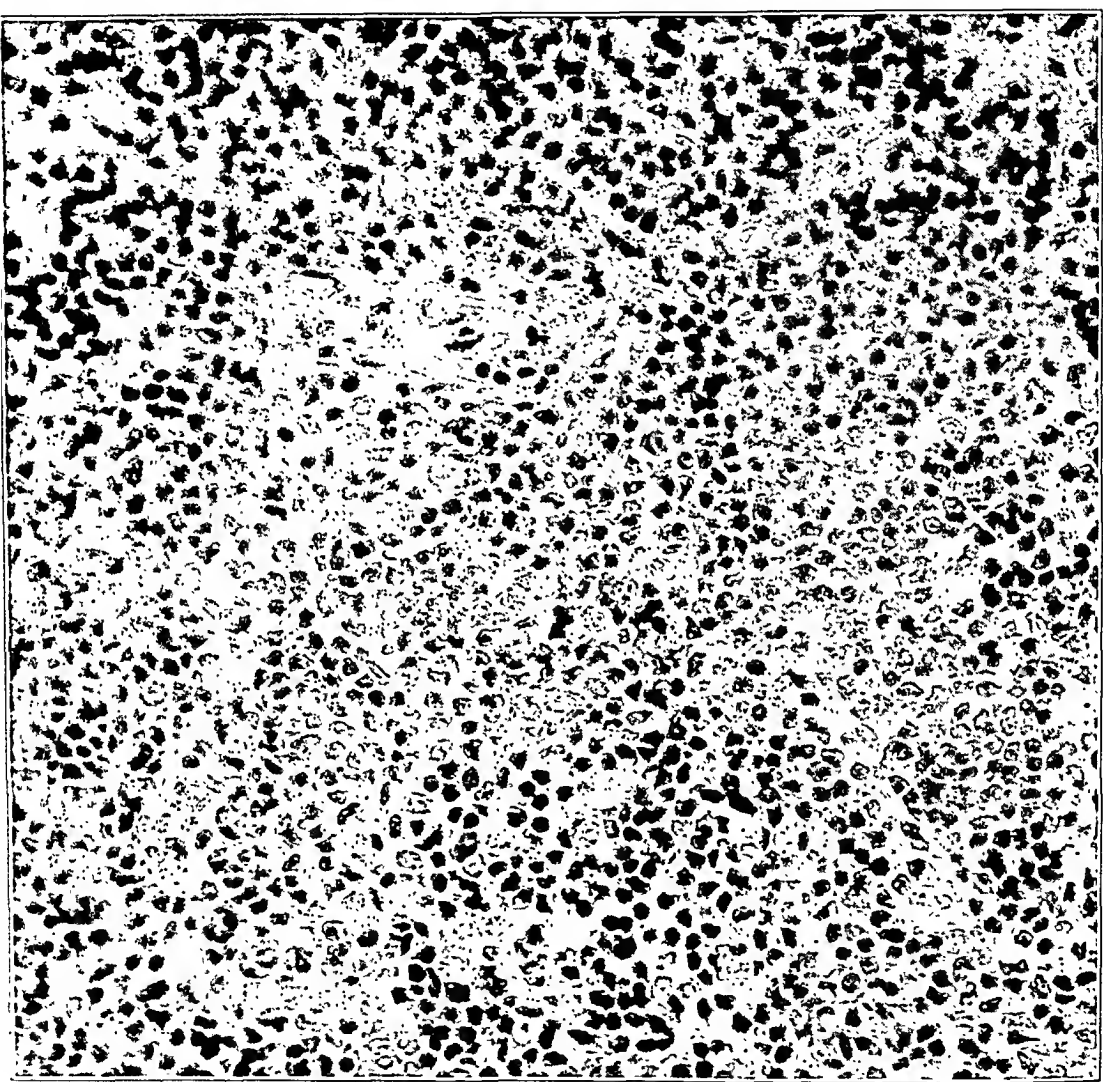


Fig. 28 (case 19).—High power photomicrograph of sympathicoblastoma, showing a cellular tumor consisting mostly of sympathogonia. A few sympathoblasts may be seen.

vesicular and the cytoplasm becomes more abundant. The cytoplasmic processes or the fibrils become prominent features. The cells are then sympathoblasts. As the cells approach the adult form, the nuclei are

When sympathoblasts are present in abundance, fibrils are usually a prominent feature (fig. 29). Rosettes are often present. The intermingling of the two types of cells, sympathogonia and sympathoblasts, forms a microscopic picture characteristic of the differentiated sympathicoblastoma (fig. 30). Well formed rosettes were not numerous

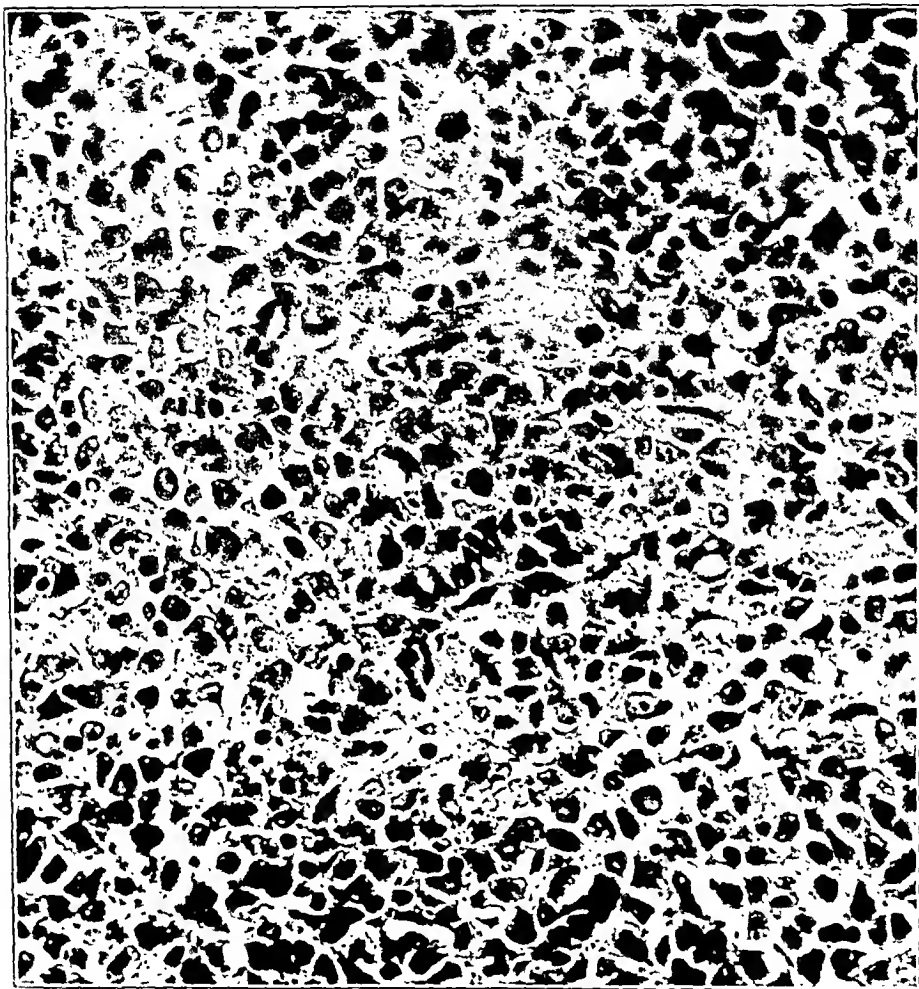


Fig. 30 (case 21).—High power photomicrograph of a sympathicoblastoma, showing sympathogonia and sympathoblasts.

in any of these tumors. Mitotic figures though present were not numerous.

When the adult ganglion cell is present, the tumor is easily identified (fig. 31). The gangliosympathicoblastomas usually contain less differentiated cells as well. In this section reactive bone and fibrosis were marked features.

of a more clearly differentiated and less malignant form than were the other tumors.

Table 5 indicates that sympathicoblastoma is radiosensitive. The patient in case 17 was well without recurrence of symptoms seven years after the operation. Irradiation was given postoperatively. Stewart<sup>29</sup> and also Colville and Willis,<sup>30</sup> have observed that neuroblastoma (sympathicoblastoma) responds to irradiation. This radiosensitivity is a characteristic of two other neuroblastic tumors, retinoblastoma (Moore<sup>31</sup>) and medulloblastoma (Cutler, Sosman and Vaughan<sup>32</sup>), both of which resemble sympathicoblastoma in histologic appearance.

*Ewing's Sarcoma.*—No tumors were found in this series which could unquestionably be diagnosed as Ewing's sarcoma of the spine. The remarkable similarities between this tumor and sympathicoblastoma

TABLE 5.—*Duration of Life of Patients and Type of Treatment in Cases of Sympathicoblastoma*

Case No.	Duration of Symptoms Prior to Treatment, Months	Duration of Life After Treatment, Months	Treatment	Result
12	..	72	Excision; irradiation	Patient died
17	5	84	Excision; irradiation	Patient well 1933
16	18	43	Excision; irradiation	Patient died
10	6	42	Excision	Patient died
13	2	21	Excision; irradiation	Patient died
11	6	12	Excision; irradiation	Patient died
19	1	7	Excision	Condition of patient improved 1937
21	18	4	Excision	Condition of patient improved 1937
15	6	0	None	Patient died
14	60	0	None	Patient died
20	5	..	?	Patient died
18	8+	?	Excision	No follow-up

account in some measure for this difficulty. The microscopic picture of Ewing's sarcoma and that of sympathicoblastoma are strikingly similar, and by the ordinary staining methods differentiation between the two is difficult. The reticulum cell variant of Ewing's sarcoma is not unlike a sympathicoblastoma in which sympathoblasts predominate. In addition, both types of tumor may respond to high voltage roentgen therapy. Both types of tumor also have a tendency to metastasize to one or more bones, to the lungs or to the lymph nodes.

29. Stewart, F. W.: Radiosensitivity of Tumors, *Arch. Surg.* **27**:979 (Dec.) 1933.

30. Colville, H. C., and Willis, R. A.: Neuroblastoma Metastases in Bones, with a Criticism of Ewing's Endothelioma, *Am. J. Path.* **9**:421, 1933.

31. Moore, R. F.; Stallard, H. B., and Milner, J. G.: Retinal Gliomata Treated by Radon Seeds, *Brit. J. Ophth.* **15**:673, 1931.

32. Cutler, E. C.; Sosman, M. C., and Vaughan, W. W.: The Place of Radiation in the Treatment of Cerebellar Medulloblastoma: Report of Twenty Cases, *Am. J. Roentgenol.* **35**:429, 1936.

seventh cervical vertebra was removed. The tumor had eroded the intervertebral foramen as it passed out into the neck. The condition of the patient improved after the operation, but symptoms of compression of the spinal cord again developed in the fall of 1935. Roentgen examination in November 1935 revealed increased density in the bodies of the seventh cervical and first thoracic vertebrae, with slight destructive changes and a slight periosteal reaction. There also appeared to be a mass anterior to the vertebral bodies which displaced the trachea forward. Roentgen examination in February (fig. 32) revealed an increase in the size of the prevertebral mass. Laminectomy was again performed in February, but no tumor was found. The patient's condition did not improve, and he died of tracheal obstruction in September. At autopsy a friable hemorrhagic tumor was found overlying the bodies of the cervical vertebrae. Though it was not encapsulated, it was fairly well circumscribed, almost polypoid in appearance. The vertebral bodies were eroded and invaded. The tumor extended into the spinal canal and compressed the spinal cord. It encircled the esophagus and the trachea and extended downward into the upper mediastinum. The subclavian and jugular veins



Fig. 32 (case 10).—Sympathicoblastoma in the cervical region. The roentgenogram shows increased density of the bodies of the seventh cervical and first thoracic vertebrae, with slight destructive changes in the anterior portions of the bodies of these vertebrae. A paravertebral mass is visible which has displaced the trachea anteriorly. A laminectomy has previously been done.

were invaded. The lungs contained metastatic nodules. Microscopic examination revealed a cellular tumor invading muscle and divided into large alveoli by fibrous septums. The cells were almost entirely sympathogonia. Necrotic areas, rare, poorly formed rosettes and occasional mitotic figures were present.

CASE 11.—A white woman aged 30 complained of pain in the back present for six months and of numbness of the legs and feet present for two weeks. On examination, tenderness was elicited over the sixth and seventh thoracic vertebrae and a partial spastic paralysis, with hypoesthesia, was present below the level of the seventh rib. Roentgen examination in December 1930 showed destruction and partial collapse of the body of the sixth thoracic vertebra and destruction of the spinous processes and the laminae of the thoracic vertebrae from the fifth to the seventh. At operation in the same month an extradural tumor was found destroying bone, pressing on the spinal cord and extending into the mediastinum.



fibrosis and an occasional giant cell were present. Numerous fibrils were seen about some of the ganglion cells. Some of these cells were embedded in bone, and a few sympathoblasts were present. An occasional mitotic figure was seen (fig. 31).

CASE 15.—A white man aged 45 complained of pain in the lower part of the back following an injury five months before and of pain in the chest and bloody sputum present for one month. A tumor had been noticed in the left axilla for one month. Roentgen examination revealed destruction of the left transverse process and of the left side of the body of the fourth lumbar vertebra. There were also osteolytic changes in the ribs and in the skull. At autopsy in October 1931 a tumor of the left adrenal medulla was found, with metastases to the spine, the ribs, the skull, the brain, the lymph glands and the lungs. Microscopic examination showed a cellular tumor composed principally of sympathoblasts, divided by fibrous septums into alveoli. Most of the nuclei were elongated and lay parallel to each other in small groups. An occasional mitotic figure was found, as well as an occasional poorly formed rosette.

CASE 16.—A white man aged 29 complained of pain in the back following an injury eighteen months before and of gradually increasing symptoms of compression of the spinal cord ending in complete paralysis of both lower extremities three days before roentgen examination. There were sensory changes at the level of the eighth thoracic segment. Roentgen studies in September 1929 showed osteosclerosis of the body of the tenth thoracic vertebra, with a fusiform paravertebral mass (fig. 25). Laminectomy in the same month disclosed an extradural tumor adherent to the laminae of the ninth thoracic vertebra and pressing on the spinal cord. Roentgen therapy was employed postoperatively. The condition of the patient was improved by the operation. In June 1930 a hard mass above the left clavicle was noted, which seemed to be attached to the spine. Roentgen examination at this time revealed osteosclerosis of the body of the sixth cervical vertebra. The patient died in April 1933. Permission for autopsy was not obtained. Microscopic examination revealed a cellular tumor composed almost entirely of sympathoblasts and divided by numerous fibrous septums. The nuclei were large and vesicular, with large nucleoli. The cytoplasm, though not abundant, was well marked and extended into short processes. There were present a few groups of sympathogonia with parallel nuclei. No rosettes were seen. Mitotic figures were rare.

CASE 17.—A white woman aged 17 complained of pain in the left leg present for five months and of weakness of the left leg, numbness of the left buttock and difficult urination present for six weeks. The fifth lumbar vertebra was tender, and there was a mass over the dorsum of the sacrum. Roentgen examination in April 1931 showed destruction of the laminae and transverse processes of the left sacral vertebrae from the second to the fifth. At operation in the same month an extradural tumor was found in the sacral canal which extended into the lumbar canal and out through the anterior sacral foramen. It was partially removed, and irradiation was given postoperatively. The patient was well in 1938, without recurrence of the symptoms. Microscopic examination revealed a cellular tumor invading muscle. Both sympathogonia and sympathoblasts were present. Cytoplasmic fibrils were present in abundance. Groups of deeply staining, elongated, parallel nuclei were frequent. No well formed rosettes were seen, and mitotic figures were rare.

CASE 18.—A white man aged 47 complained of loss of control of the bladder present for eight months, numbness of the feet present for two months and difficult

nerve sheaths may be diagnosed by the fact that the neurologic features are prominent and that the changes in bone, if present, are either slight or characteristic. This does not apply to malignant tumors of this type or to certain varieties of glial tumors. The latter tumors are uncommon.

*Perineurial Fibroblastoma (Neurinoma).*—This tumor occurs in the spine with a frequency approximately equal to that of meningeal tumors, and each is more common in this region than is glioma. Perineurial fibroblastoma (neurinoma) occurs more frequently in the lumbar and the sacral region than in other parts of the spine. The benign form is a firm, encapsulated intradural or extradural tumor attached to a nerve root. It may or may not extend outside the spinal canal in hour-glass fashion. It produces symptoms of compression of the spinal cord or of the cauda equina, often associated with pain at the nerve roots. Even when changes in bone occur, pain in the back is not a common complaint, though localized tenderness may be present. Camp, Adson and Shugrue pointed out that this tumor more commonly than any other glial or nerve sheath tumor produces changes in the vertebral column. According to their studies, the pedicle, the laminae and the body of the vertebra are eroded in the order mentioned. The transverse process may be eroded by an extraspinal portion of the tumor. Figure 33 shows erosion of the pedicles and laminae of the fifth lumbar vertebra. A lateral view in this case showed a circular defect 3 cm. in diameter at the right intervertebral foramen. The erosion caused by these benign tumors is smooth and must be distinguished from the destruction of bone produced by invasive tumors. Slight erosions are easily overlooked. Measurement of the spinal canal reveals changes in bone in a large number of the cases. Basing their studies on a series of tumors of the spinal cord, Elsberg and Dyke<sup>33</sup> were able by this method to detect changes in 42 per cent of 67 cases and in 70 per cent of 20 cases in which the tumors were between the tenth thoracic vertebra and the first sacral vertebra. A neurinoma may occasionally contain calcified areas which are visible in the roentgenogram, but this feature is much more characteristic of meningiomas.

In this series there were 8 benign neurinomas which produced changes in bone detected in the roentgenogram or at operation. No attempt was made with these or with any of the glial or nerve sheath tumors to detect slight changes by measurement of the spinal canal.

Sarcoma of a nerve sheath is not so clearly characteristic in the roentgenogram as is neurinoma. There were 4 such tumors in this

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33. Elsberg, C. A., and Dyke, C. G.: Diagnosis and Localization of Tumors of the Spinal Cord by Means of Measurements Made on the X-Ray Films of the Vertebrae, and the Correlation of Clinical and X-Ray Findings, *Bull. Neurol. Inst. New York* 3:359, 1934.



Fig. 34.—Sarcoma of the neural sheath involving a thoracic vertebra. The roentgenogram shows destruction, with partial collapse, of the body of the eighth thoracic vertebra. (Case of Dr. E. T. Wentworth, Rochester, N. Y.)



Fig. 35.—Meningeal fibroblastoma. The roentgenogram shows a calcified mass lateral to the fourth cervical vertebra which has destroyed the pedicle and transverse process in this region. (Case of Dr. A. Wilson Smith, Chicago.)

other of which invaded and destroyed bone (fig. 37). The remaining tumor was a primitive neuroepithelioma (fig. 38) which occurred ventral to the sacrum, causing destruction of that bone.

In general, it may be said that the glial tumors which cause osseous changes are of the less differentiated, extramedullary type and that they occur in the lumbar and sacral regions.

#### TERATOID AND TERATOLOGIC TUMORS

Sacrococcygeal tumors are often grouped together. Ependymoma, chordoma, neuroepithelioma and giant cell tumor are sometimes described

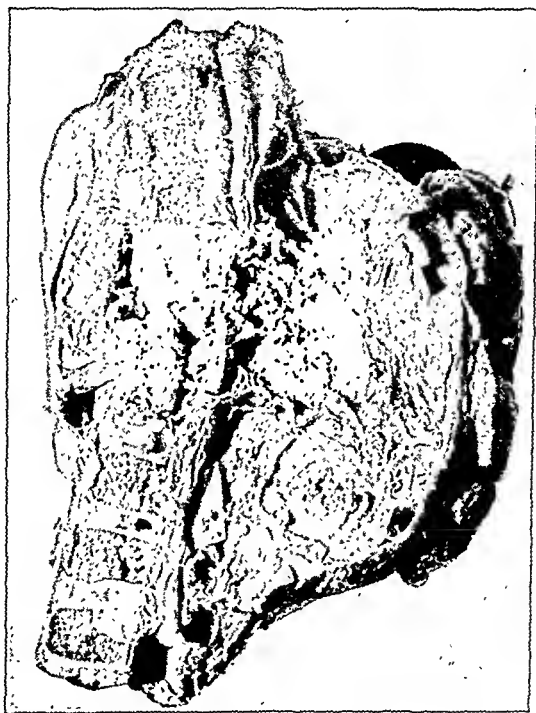


Fig. 37.—Astroblastoma in the dorsolumbar region. The photograph shows a longitudinal section of the lesion at autopsy. There is a large paravertebral mass dorsal to the spine and a smaller ventral mass. Six vertebrae are either partially or completely destroyed. At postmortem examination the spinal cord could be traced as a slender fibrous cord traversing the mass. (Case of Dr. Horace B. Davidson, Columbus, Ohio.)

under this heading. We have mentioned these tumors elsewhere. The dorsal tumors are usually dermoid cysts or teratomas. Giant cell tumor and ependymoma usually occur within the body of the sacrum. Ventral tumors are numerous and varied. Teratoma and chordoma are common in this region.

## DIFFERENTIAL DIAGNOSIS

Spinal tumor is frequently diagnosed as tuberculosis of the spine. It may be impossible to differentiate the one from the other by roentgen examination. This is true particularly in regard to the malignant tumors. Certain points, however, may be of use. Fray has pointed out that a vertebral body destroyed by malignant disease is apt to collapse uniformly, producing an "accordion effect." A triangular compression of a vertebral body is more common in tuberculosis. This variation in the type of collapse accounts for the fact that a gibbus is usually less marked in a neoplastic lesion than in a tuberculous lesion. A firm type of tumor, of course, may destroy a vertebral body and yet prevent any appreciable collapse. A characteristic of tuberculosis is destruction in the anterior portion of adjoining vertebral bodies, a very uncommon finding with spinal tumor. Compere and Garrison<sup>34</sup> stated that they have never seen tuberculosis primarily affect the neural arch or its appendages. These parts are frequent sites of neoplastic growth. Tuberculosis shows little tendency to regeneration of bone (Compere and Garrison), a marked feature with some tumors, especially after irradiation. A paravertebral shadow when it is not distinctive of some particular type of tumor is of no diagnostic value. The presence or absence of the intervertebral disk is likewise of little help. In some cases it may be found necessary to attempt an aspiration to obtain material for culture or for microscopic examination. In general, however, it may be said that in the absence of compression of the spinal cord, which is a symptom requiring operative relief, it is best to treat the doubtful condition by rest and by irradiation.

Pyogenic osteomyelitis of the spine should not, as a rule, be confused with neoplasm. The history of a preceding infection, the acute febrile state and the early destruction of the intervertebral disk should establish the diagnosis. Acute osteomyelitis of the spine is uncommon compared with tuberculosis.

The lesions of the spine which also must be borne in mind are those of typhoid fever, of syphilis, of fungus infection and of osteomalacia.

In any case of lesion of the spine in which the diagnosis is doubtful it is well to make a roentgen examination of the entire skeleton. The possibility of the presence of syphilis may be ruled out by serologic tests or by the response to specific therapy. The urine should be examined for Bence Jones bodies. The response to roentgen therapy may be helpful in the diagnosis.

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34. Compere, E. L., and Garrison, M.: Correlation of Pathologic and Roentgenologic Findings in Tuberculosis and Pyogenic Infections of the Vertebrae: Fate of the Intervertebral Disk, *Ann. Surg.* 104:1038, 1936.

A glial or nerve sheath tumor of the spinal cord may involve the vertebral column. A meningeal tumor usually affects the thoracic or the cervical region and may be visible in the roentgenogram, either because of erosion of bone or because of calcification in the tumor. Neurinoma or neurofibroma of a spinal nerve root more often causes erosion of bone than does a meningeal tumor. Neurinoma is most common in the lumbar and the sacral regions. This benign tumor attached to a nerve root may slowly erode bone, the pedicle, the laminae and the body of the vertebrae being affected in the order mentioned. Erosion is more rapid and more pronounced with a malignant nerve sheath tumor affecting the roots of the spinal nerves. Glial tumors producing changes in bone are rare. They are usually primitive neuroepitheliomas or ependymomas. In the sacrococcygeal region a benign or malignant teratoma may erode bone.

*Periosteal Regeneration.*—According to Duhamel,<sup>4</sup> Syme,<sup>5</sup> Ollier,<sup>6</sup> Axhausen,<sup>7</sup> Haas,<sup>8</sup> Mayer and Wehner,<sup>9</sup> Phemister,<sup>10</sup> Berg and Thalhimer,<sup>11</sup> Rohde,<sup>12</sup> Blaisdell and Cowan,<sup>13</sup> Mock,<sup>14</sup> Ham,<sup>15</sup> Smith,<sup>16</sup> Haldeman,<sup>17</sup> Leadbetter,<sup>18</sup> Riess,<sup>19</sup> Schepelmann,<sup>20</sup> Bisgard<sup>21</sup> and many others, periosteum and endosteum are definite organs for the formation and repair of bone. Osteoblasts, according to this theory, never come from adult bone cells, but arise from the cells of the periosteum and, to a lesser extent, from the endosteum.

*Osteoblastic Regeneration.*—Goodsir,<sup>22</sup> Macewen,<sup>23</sup> Brown and Brown,<sup>24</sup> Moore and Corbett,<sup>25</sup> Davis and Hunnicutt,<sup>26</sup> Gallie and

4. Duhamel du Monceau, H. L.: *On the Formation of Bones in Animals and of Wood in Trees*, Rec. périod. d'obs. de méd., de chir. et pharm. **7**:161, 1757.

5. Syme, J., cited by Keith, A.: *Growth and Regeneration of Bone*, Brit. J. Surg. **5**:685-693, 1918.

6. Ollier, L.: *Traité expérimental et clinique de la régénération des os et de la production artificielle du tissu osseux*, Paris, V. Masson & Son, 1867, vol. 1 and 2.

7. Axhausen, G.: *Die histologischen und klinischen Gesetze der freien Osteoplastik auf Grund von Tierversuchen*, Arch. f. klin. Chir. **88**:23-145, 1908.

8. Haas, S. L.: *Regeneration of Bone from Periosteum*, Surg., Gynec. & Obst. **17**:164-174, 1913.

9. Mayer, L., and Wehner, E.: *Experimental Study of Osteogenesis*, Am. J. Orthop. Surg. **12**:213-244, 1914.

10. Phemister, D. B.: *Fate of Transplanted Bone and the Regenerative Power of Various Constituents*, Surg., Gynec. & Obst. **18**:303-333, 1914.

11. Berg, A. A., and Thalhimer, W.: *Regeneration of Bone*, Ann. Surg. **67**:331-347, 1918.

12. Rohde, C.: *Does Bone Form from Osteoblasts or from Metaplasia of Surrounding Connective Tissue?* Surg., Gynec. & Obst. **41**:740-772, 1925.

13. Blaisdell, F. E., and Cowan, J. F.: *Healing of Simple Fractures*, Arch. Surg. **12**:619-634 (March) 1926.

14. Mock, H. E.: *Periosteal Transplants in Delayed Union, Non-Union and Loss of Bone Substance*, Surg., Gynec. & Obst. **46**:641-657, 1928.

15. Ham, A. W.: *Histological Study of Early Phases of Bone Regeneration*, J. Bone & Joint Surg. **12**:827-844, 1930.

16. Smith, F. D.: *Periosteal Regeneration of Bone*, Surg., Gynec. & Obst. **20**:547-552, 1915.

17. Haldeman, K. O.: *Role of Periosteum in Healing of Fractures*, Arch. Surg. **24**:440-450 (April) 1932.

18. Leadbetter, G. W.: *Periosteum*, Arch. Surg. **22**:754-785 (May) 1931.

19. Riess, E.: *Experimentelle Studien über die knochenbildende Kraft des Periostes*, Arch. f. klin. Chir. **129**:750-757, 1924.

20. Schepelmann, E.: *Freie Periostverpflanzung*, Arch. f. klin. Chir. **101**:499-510, 1913.

21. Bisgard, J. D.: *Experimental Studies of Reparative Costal Chondrogenesis and of Transplanted Bone*, Surg., Gynec. & Obst. **58**:817-822, 1934.

22. Goodsir, J.: *Anatomical Memoirs of John Goodsir*, edited by William Turner, Edinburgh, A. & C. Black, 1868, vol. 2.

23. Macewen, W.: *Growth of Bone*, Glasgow, J. Maclehose & Sons, 1912.

## TRANSPLANTATION OF BONE

Investigators have differed in their opinions concerning the fate of autoplasmic bone grafts, according to the theory of osteogenesis they have supported. Those who have concluded that bone in itself is osteogenic have interpreted their results to show that bone grafts grow; those who have concluded that periosteum is the source of new bone have stated that bone grafts die and are absorbed or may act as a framework for new bone, and those who have been convinced that connective tissue forms new bone have stated that the graft acts as a source of calcium salts, which stimulates metaplasia in the connective tissue.

Macewen was able to show phenomenal results in his experiments. Free grafts of bone grew, chips of bone produced new bone and chips implanted into muscle tissue produced large plaques of new bone. Phemister, Haas,<sup>41</sup> Axhausen, Thalheimer and Brooks<sup>42</sup> have published work which seems to show that free transplants of bone act as a source of regeneration and are not merely a trellis into which new bone grows from neighboring sources.

McWilliams,<sup>43</sup> Phemister, Rohde, Ham, Pollack<sup>44</sup> and others have adopted the very reasonable view that the success or failure of a graft of bone or periosteum, or both, depends on the rapidity with which the graft is able to establish a new and adequate blood supply. According to this view, small bone grafts do not need a periosteal covering because they easily become vascularized, whereas larger grafts may fail because of a lack of this vascularity. Periosteum on these larger grafts may insure success because of the preformed vascular channels present.

Brooks and Hudson, using dogs, obtained success with 84 per cent of autoplasmic grafts of the ulna, as compared with success with 76 per cent of homoplasmic grafts in the same region. They concluded that the compatibility of tissues is an important factor in the success of these grafts. They used intravital staining to demonstrate the formation of new bone.

Camitz, Holmgren and Johansson<sup>45</sup> were successful with homologous transplants in dogs and found that all elements of the graft were concerned in healing and in the regeneration of bone.

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41. Haas, S. L.: Regeneration of Bone and Cartilage at the Costochondral Junction, *Surg., Gynec. & Obst.* **19**:604-617, 1914.

42. Brooks, B., and Hudson, W. A.: Studies on Bone Transplantation, *Arch. Surg.* **1**:284-309 (Sept.) 1920.

43. McWilliams, C. A.: Periosteum in Bone Transplantation, *Surg., Gynec. & Obst.* **18**:159-169, 1914.

44. Pollack, W. E.; McKenney, P. W., and Blaisdell, F. E.: Viability of Transplanted Bone, *Arch. Surg.* **18**:607-623 (Feb.) 1929.

45. Camitz, H.; Holmgren, H., and Johansson, H.: Study of Bone Transplants, *Acta chir. Scandinav.* **75**:1-67, 1934.



discussed these observations and felt that the phenomena could be explained only by the hypothesis of Leriche, that bone is formed in the presence of reacting connective tissue and of excess calcium salts. Asami and Dock had previously studied heterotopic formation of bone in the urinary tract, stating that new bone is formed by metaplasia of fixed connective tissue cells. Neuhoof, in his extensive work with fascial transplants, found that there was early disintegration followed by replacement with firm fibrous tissue. Bone frequently was formed, especially in the bladder. He also explained this osteogenesis on the basis of metaplasia in the connective tissue. Huggins<sup>51</sup> concurred in the observations of the effect on the formation of bone when bladder mucosa was transplanted into connective tissue. He found that bladder mucosa normally secretes calcium and phosphorus, and he indorsed the theory of Leriche. Roome and McMaster<sup>52</sup> found that venous stasis favored the laying down of heterotopic bone. They further observed that this new bone tended to be absorbed subsequently. This coincides with the theory of Wolff<sup>52</sup> which stated that bone is anatomically adapted to its function, and with the idea of Roux,<sup>53</sup> which is that functionless bone is absorbed.

#### CHEMICAL INHIBITION OF RIB REGENERATION

Head,<sup>54</sup> in 1927, was the first to advocate the use of chemical inhibition of rib regeneration in thoracic surgery as an aid to collapse, exposure and drainage. In an experimental series he used a stick of silver nitrate, a 50 per cent solution of silver nitrate, concentrated chromic acid and Zenker's solution. He found that silver nitrate gave extensive necrosis with a high incidence of pleural perforation and death. Chromic acid gave satisfactory inhibition of regeneration for four weeks, and Zenker's solution, for six weeks. It is interesting to note that Head stated that chemical inhibition of rib regeneration is contraindicated in cases of extrapleural thoracoplasty for surgical collapse in pulmonary tuberculosis. He based this statement on the assumption that since the mediastinum is not fixed, permanent mobilization of the chest wall would produce paradoxical respiration in the collapsed lung, with a consequent reduction in the already compromised vital capacity.

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51. Huggins, C. B.: Formation of Bone Under the Influence of Epithelium of the Urinary Tract, *Arch. Surg.* **22**:377-408 (March) 1931.

52. Wolff, J.: *Das Gesetz der Transformation der Knochen*, Berlin, A. Hirschwald, 1892.

53. Roux, W.: Die Entwicklungsmechanik, ein neuer Zweig der biologischen Wissenschaft, in *Vorträge und Aufsätze über Entwicklungsmechanik*, Leipzig, Wilhelm Engelmann, 1905, vol. 1, pp. 1-283.

54. Head, J. R.: Prevention of Regeneration of the Ribs, *Arch. Surg.* **14**:1209-1215 (June) 1927.

Haight<sup>60</sup> in 1936 stated that as a matter of routine he applies solution of formaldehyde U. S. P. diluted 1 to 10 to the periosteal beds and is thereby able to lengthen the interval between the stages of thoracoplasty. He concluded that collapse is improved and subsequent stages are facilitated.

#### RIBS OVERLYING EMPYEMA CAVITIES

Bisgard<sup>61</sup> in 1933 called attention to the fact that the external form of ribs overlying empyema cavities is changed, and that there is new bone formation along the inferior and internal aspect of these ribs. He noted this change even in acute empyema and concluded that these changes could be utilized as a means of estimating the size of empyema cavities by roentgenograms. He explained this proliferation of bone on the assumption that the infected pleura causes periostitis, which stimulates osteogenesis, and stated that the successive layers of new bone indicate a series of such stimuli. Bisgard<sup>61</sup> invoked Wolff's law of functional adaptation to explain the change in contour of the ribs, believing that the centripetal pull of the contracting pleural scar was the force modifying costal architecture.

#### PROBLEM AND PURPOSE OF THE STUDY

The process of normal osteogenesis is not known, and the sequence of events in osseous regeneration is poorly understood. The literature on these two problems is voluminous and conflicting even in the fundamental concepts. However, Ham's histologic studies of the early phases of the regeneration of bone may be accepted as reflecting the usually adopted beliefs. Ham<sup>13</sup> found that after fracture of the rabbit's rib the adult bone cells died for a distance of 1 to 5 mm. Fragments of bone died also, and this is contrary to the view of Macewen, who said that fragments become centers of osteogenesis. Ham found the lacunas empty or containing pyknotic nuclei. Beyond this area the adult bone cells showed no evidence of proliferation. These observations were borne out by those of Blaisdell and Cowan, Berg and Thalhimer, Mayer and Wehner, Rohde and Mallory. Ham noted that the periosteal osteoblasts after fracture showed mitosis and that gross examination of the periosteum showed it to be thicker and more cellular. The external layers of cells were rapidly dividing, whereas the deeper layers were laying down a cartilaginous matrix. These layers were solid masses of differentiating cells, without blood vessels. Somewhat deeper, new bone formation was found, and here vascularity was noted. Ham pos-

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60. Haight, C.: Complementary Anterior Thoracoplasty for Pulmonary Tuberculosis, *J. Thoracic Surg.* 5:453-470, 1936.

61. Bisgard, J. D.: Ribs Overlying Empyema Cavities, *Arch. Surg.* 27:941-959 (Nov.) 1933.

the periosteum could be stripped from the ribs, the dogs were young. A few old dogs were used in order to determine the effect of the age factor on the regeneration of bone. All operations were performed with the dogs under pentobarbital sodium anesthesia, 35 mg. per kilogram of body weight being administered intraperitoneally in aqueous solution. The operative site was shaved and prepared with iodine and alcohol. Strict aseptic precautions were used in all operations. In some instances a long oblique muscle-splitting incision was used to expose several ribs, while in others individual incisions were made over each rib which was to be attacked. In the thoracoplasties and similar operations adjacent ribs were used, but in all other experiments alternate ribs were left intact. In many of the dogs three alternate ribs on the right and three on the left were attacked. Linen and silk were used as suture material. When gross infection followed the operation the dog was not included in the series. Roentgenograms of the thorax were taken before the operation, immediately after the operation and at intervals during the period of observation. The dogs were killed at intervals varying from four weeks to four months, and the specimens were then obtained, with several normal ribs on each side for purposes of control. In most instances the specimens were described grossly, roentgenograms were then made and in some cases photographs of the dried specimens were taken. Usually, however, after the roentgenograms were taken the specimens were fixed in solution of formaldehyde, decalcified and sectioned. Decalcification was accomplished with (1) 5 per cent nitric acid, (2) 10 per cent nitric acid and 80 per cent alcohol in equal parts and (3) 5 per cent hydrochloric acid. The latter solution was found to be preferable because the tissues could be cut with greater ease and because the xanthoprotein formed by nitric acid seemed to interfere with staining reactions. All sections were stained with hematoxylin and eosin. Dogs dying within one month were included only if the specimens could be obtained before postmortem autolysis had developed. These early specimens were not used in computing the final results but were included simply to throw some light on the early processes of regeneration of bone.

Several attempts were made to use intravital staining of new bone by the intraperitoneal injection of 10 cc. of a saturated aqueous solution of sodium alizarin sulfonate twice weekly, but in no instance was the attempt successful.

The clinical data are based on patients from the University Hospital, who had empyema thoracis or pulmonary tuberculosis requiring surgical collapse. The specimens were prepared in the same manner as those from the experimental animals.

## EXPERIMENTAL DATA

### ROLE OF PERIOSTEUM IN RIB REGENERATION

*Subperiosteal Rib Resection.*—In 15 dogs, a 3 cm. segment of rib was excised subperiosteally. The remaining periosteal bed was not sutured into tubular form but was left as a flat strip. Specimens were obtained after eight, ten, fourteen, thirty and ninety days. The 2 eight and ten day specimens showed organizing hemorrhage in the periosteal bed, and in 1 there was very early evidence of new osseous formation. The 2 specimens obtained after fourteen days showed early regeneration of bone. In 8 of the 10 specimens obtained after one month complete regeneration had taken place, while in the other 2 there was a small central area not yet filled by new bone. The three month specimen was firmly regenerated, and on section the new bone was seen to have a normal adult type of architecture.

The microscopic sections showed new bone forming from connective tissue. In 20 per cent of the one month specimens cartilage had been formed and was

specimens, 80 per cent showed new bone being formed in the periosteum which had been separated from the rib by a muscle flap. In 60 per cent there was an incomplete bridge of new bone, and in 20 per cent the bridge had formed a complete new rib. Six of the denuded ribs were being absorbed. They were irregularly roughened, and the roentgenogram demonstrated them to be atrophic. Microscopically, when sectioned, some of them were seen to be disintegrating and to be surrounded by a dense layer of fibrous tissue (fig. 3). The three month specimen had a well developed new periosteal rib which showed an adult type of arrangement of the bone cells. The old rib was dead, and fragmentation had set in.

In 3 other dogs a flap of muscle was interposed between the rib and the periosteum in two adjacent ribs. After six weeks each of these specimens showed an incomplete bridge of periosteal new bone, and the denuded ribs were atrophic and smaller in diameter than they had been before (figs. 4 and 5).



Fig. 2.—This photomicrograph shows the dense bed of fibrous tissue formed one month after a segment of rib had been removed with its periosteum. There is no new bone formation.

*Insertion of a Foreign Body Pack Between a Rib and Its Periosteum.*—In 2 dogs the periosteum was separated from five adjacent ribs, and half of a celluloid soap dish was inserted between the ribs and the periosteum, the concavity being turned toward the ribs. These specimens were removed after six weeks. In 1 dog there were pleuropulmonary adhesions beneath the operative site. In both specimens the ribs were irregularly absorbed and were atrophic. The periosteal beds showed varying degrees of regeneration, from spurs of bone at the angles of reflection to complete solid bridges of new bone (fig. 6). This same procedure was repeated in 2 instances, a sterile gauze pack being substituted for the celluloid device and a molded mass of paraffin being used in 1 instance between the ribs and the periosteum. The specimens in which the gauze pack had been used were recovered after six weeks. In both the ribs were being absorbed and were covered by a

The specimens were recovered after four, eight, fourteen, thirty and forty-two days. After four days there were no gross changes, but microscopically there was a marked increase in the cellularity of the periosteal layer. The eight day specimen was not sectioned, because an extensive subcutaneous abscess developed, and the rib was denuded of its periosteum for 3 cm. on each side of the drill hole. After two weeks there was a moderate amount of new bone around the drill

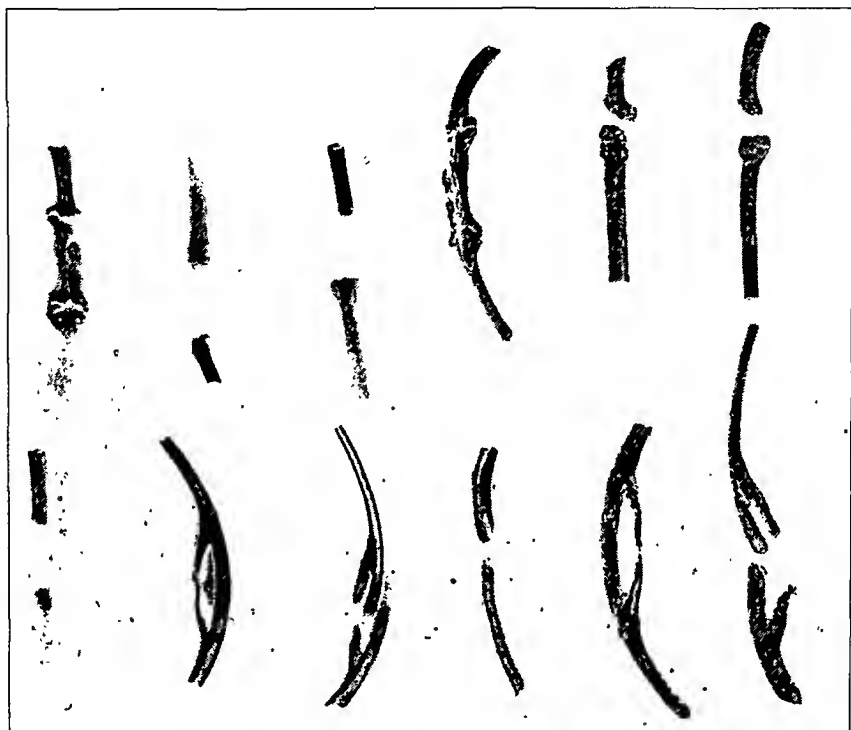


Fig. 4.—The roentgenogram at the left shows the progress of osseous regeneration after one month. In the upper left hand corner, regeneration after subperiosteal resection is seen to be almost complete. Note that regeneration is not originating from the ends of the ribs. In the specimen to the right, the periosteum was removed with the rib segment. Observe the absence of osseous regeneration and the eburnation of the rib ends. The specimen at the top on the right shows the inhibitory effect of the application of Zenker's solution to the periosteal bed. There is a small spur of new bone from the periosteum, with eburnation of the rib end. The periosteal bed of the specimen on the lower left was treated with solution of formaldehyde U. S. P. diluted to 1 to 10. Note the absence of new bone and the more nearly normal appearance of the remaining bone. To the right of it is seen the result of the interposition of a muscle flap between the rib and its periosteum. The bridge of new bone is not quite complete, and there is no atrophy, but some increased density, of the old rib. In the specimen at the bottom on the right is seen the result of fracture when the periosteum is separated from the fragments by a muscle flap. The rib ends are irregularly eroded, and there has been no attempt at healing. The periosteal bridge, again, is incomplete. The figure at the right is a photograph of the same specimens after the drying and removal of the soft tissue. All of these specimens are from the same dog and represent alternate ribs, three on the right and three on the left.

hole. This new bone almost completely surrounded the rib and apparently arose from the periosteum, blending into the surrounding fibrous tissue. After one month there was a large amount of new bone, apparently arising in a similar manner. The six week specimen showed a moderate amount of new bone, which now had taken on an adult type of architecture.

#### ROLE OF PERIOSTEUM IN THE HEALING OF COSTAL FRACTURES

*Separation of the Periosteum from the Site of the Fracture by a Flap of Muscle.*—In 15 dogs a rib was exposed and the periosteum was incised for a



Fig. 7.—This roentgenogram shows the result six weeks after the insertion of a sterile gauze pack between the periosteum and the ribs. Periosteal new bone is well shown, and there is marked atrophy of the deperiostealized ribs.

distance of 3 cm. The periosteum was then bluntly separated from the rib and a flap of viable muscle was interposed between the rib and its periosteum. Care was taken to jeopardize the blood supply as little as possible, and the trauma was minimal. After the flap of muscle had been sutured in place, a simple clean fracture of the denuded rib was accomplished over the center of the flap by means of the rib shears. The effect of this procedure, then, was to produce a fracture of the rib, the fragments being devoid of periosteum for 1.5 cm. on each side of the fracture. One specimen was obtained after eight days, 1 after ten days, 2 after fourteen days, 10 after thirty days and 1 after ninety days. In the specimens

could determine, was implanted into the abdominal wall just beneath the anterior sheath of the rectus abdominis muscle. Hemostasis was adequate. One dog died from some other cause on the ninth day. Specimens were recovered from the other animals after six weeks. The nine day specimen showed no evidences of new bone formation on gross examination, in the roentgenogram or on section. There was a dense inflammatory reaction at the site of implantation. The 6 specimens recovered after six weeks showed a nodule of new bone in every instance. The nodules ranged from 2 mm. to 2 cm. in diameter and did not tend to assume an adult type of architecture. In no instance was formation of cartilage noted (fig. 9).

#### FATE OF BONE DEVOID OF PERIOSTEAL COVERING

*Deperiostealized Ribs.*—These data are drawn from experiments cited in other connections in this paper, and the procedures need not be described in detail again.



Fig. 8.—This roentgenogram shows the result of an experiment in which, six weeks previously, the intercostal bundles were carefully dissected away from these ribs, leaving the periosteal covering intact. A sterile gauze pack was then inserted between these periostealized ribs and the muscle bundles. A draining sinus formed in the wound, from which bony spicules were extruded. Solution of continuity of ribs is shown with adjacent periosteal new bone, probably stimulated by the local irritation of the pack.

Briefly, in 38 dogs ribs were divested of their periosteal covering and separation was maintained by muscle grafts or by foreign body packs. The ribs were studied microscopically and by roentgenogram at intervals varying from eight days to six weeks. In each instance there was death of the bone with slowly progressive atrophy and absorption by adjacent granulation tissue, which grew in and attempted to revascularize the dead bone. In no case was there definite evidence of new bone developing from the old, although new connective tissue was abundant.

## EFFECT OF AN UNDERLYING CAVITY ON FORMATION OF BONE

*Separation of Periosteum-Covered Ribs from the Intercostal Bundles by Foreign Body Packs.*—In an effort to determine whether or not bone will proliferate, as does pleura, in an attempt to obliterate an adjacent cavity, the following experiments were carried out: In 6 dogs the intercostal bundles were carefully dissected from six adjacent ribs, the periosteal covering being left intact. A portion of a celluloid soap dish was then inserted between the endothoracic fascia and the periostealized ribs. Three of the dogs died of erosion of the pleura, pleural effusion and pulmonary collapse. After six weeks the remaining dogs were killed. In 1 dog thickening of the parietal pleura beneath the foreign body had developed. In every instance the ribs were found to be covered by granulation tissue, and nodules of new bone had developed over the surface, apparently growing from



Fig. 10.—This photomicrograph of a deperiostealized graft of bone, taken six weeks after its subfascial implantation, shows it to be dead. The lacunas are empty, and fragmentation is beginning.

the haversian canals (fig. 11). Rather large spurs had formed at the edges of the artificial cavity, but there was no demonstrable evidence of formation of new bone on the inner aspect of the ribs in order to close the cavity. When sectioned, the ribs were seen to be dead, and the follicles were empty. The dead bone was being vascularized and absorbed by adjacent new granulation tissue. In one instance the artificial cavity contained a caseous white material. In the others it contained serous fluid. Aspiration had been necessary in order to remove this fluid on several occasions during the course of the experiment. This experiment did not fulfil its purpose, because the periosteal blood supply from the intercostal bundles was cut off, and apparently the endosteal blood supply is insufficient to maintain viability in the dog's rib.



of solution of formaldehyde the periosteal bed most often contained a mucoid material of gelatinous consistency. In no instance was there periosteal new bone, and in only 1 instance was there a spur from the end of the rib (fig. 12).

*Use of Solution of Formaldehyde in Periosteal Bed After Thoracoplasty.*—In 5 dogs a modified thoracoplasty was done, four, five or six ribs being excised subperiosteally. The ends of the ribs and the periosteal beds were then treated with solution of formaldehyde U. S. P. diluted 1 to 10. In 3 of the dogs multiple stage procedures were attempted, but the animals died after the second stage. In 1 instance death was due to pleural perforation by the sharp end of a rib. One specimen was obtained after two months. There was no osseous regeneration and but little spur formation. The other specimen was obtained after four months. Healing had taken place by the formation of dense fibrous tissue. There was no evidence of new bone formation. In these animals, as compared with those on

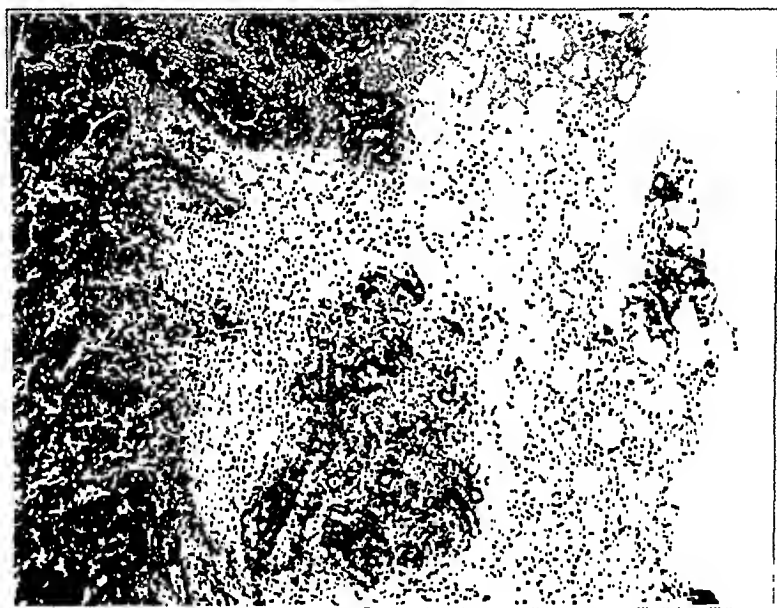


Fig. 12.—This photomicrograph shows granulation tissue and new fibrous tissue, demonstrated by section one month after the periosteal bed was treated with solution of formaldehyde. This reaction is less severe than that seen following the use of Zenker's solution. There is no new osseous formation.

which thoracoplasty was performed without treatment, wound healing was slightly delayed, but this delay was not more than three or four days. In the dogs treated with solution of formaldehyde dyspnea and paradoxical respiratory motion were observed to disappear much earlier than in the untreated dogs. Apparently this resulted because of the stimulation of proliferation in the connective tissue after the application of solution of formaldehyde, causing rigidity of the wall to follow during the first week. This did not interfere with collapse, however, as collapse was found to be much more nearly complete in the dogs treated with solution of formaldehyde. The latter observations cannot be supported by photographic or kymographic proof.

REGENERATION OF RIBS AFTER THORACOPLASTY  
AND RIB RESECTION

A study of roentgenograms taken after thoracoplasty shows that rib regeneration usually can be demonstrated in three or four weeks after the operation. The regeneration tends to take the form of flat sheets of bone with many synostoses, owing to the fact that the new bone is formed from the flat expanses of periosteum, which do not have their original tubular form. In some instances new bone can be demonstrated as early as two weeks after thoracoplasty, and in certain cases this new bone formation definitely interferes with surgical collapse therapy. In several cases it has been necessary secondarily to excise this regenerated bone in order to achieve adequate collapse from subsequent procedures. Probably, however, more frequent causes of revision of thoracoplasty are (1) inadequate external compression and (2) inadequate original thoracoplasty.

## INHIBITION OF REGENERATION

In a series of cases of acute and chronic empyema, abscess of the lung and surgical tuberculosis the periosteal beds have been treated with solution of formaldehyde U.S.P. diluted 1 to 10, and the effect on regeneration of bone has been observed for three months. In this series of about 12 cases, there has been no evidence of new bone formation in 10, even after three months, and this is an interval much longer than is usually allowed to elapse between stages of thoracoplasty. In 2 cases there was some regeneration after four weeks.

With empyema and abscess of the lung, in which healing is normally slow, the disadvantage of having new bone formed before the underlying cavity has closed is obvious. I have seen several cases in which the regenerating rib so tightly encircled the drainage tube as to necessitate a secondary resection.

In the cases of thoracoplasty no delay in the healing of the wound could be noticed, and thus far no contraindication to the use of solution of formaldehyde on the periosteal beds has been demonstrated.

## COMMENT

There are many factors which must be taken into consideration in explaining the various conflicting reports found in the literature, and it is probable that when judged by the same criteria these results could be brought into accord. For example, in experimental work the age of the animal is very important, as is the degree of operative trauma to the local vascular supply. Also, in speaking of free bone grafts, it is necessary to consider the size, because whereas small grafts may

erties under proper conditions of vascularity and availability of calcium. This explains the phenomenon of heterotopic bone formation and may explain the growth of free bone grafts, although the exact role of endosteum and the haversian system cannot properly be evaluated.

The removal of periosteum together with a rib segment effectually inhibited osseous regeneration, and there was no attempt to bridge the defect. The ends of the ribs became rounded, and the marrow cavities were sealed off by fibrous tissue. This probably illustrates the development of nonunion and pseudoarthrosis following a fracture in which the fragments are separated by periosteum over their ends or by interposed soft tissue.

Interposition of a muscle flap or of a foreign body pack between a rib and its periosteum resulted in absorption of the denuded rib and formation of a new rib in the periosteal bed. This indicates not only that the periosteum is capable of laying down new bone but that its normal function is to supply the bone with adequate nourishment. This is borne out by the fact that similar osseous necrosis resulted from destroying the intercostal blood supply to the periosteum. The denuded bone first became atrophic and then became covered by a layer of granulation tissue,<sup>64</sup> which began the work of fragmenting and absorbing the dead bone.

Osseous, periosteal and osteoperiosteal implants into muscle grew with varying degrees of success, seemingly in direct ratio to the ease and speed with which a new blood supply was established. Periosteal grafts grew more frequently than did osseous grafts, as might be expected because of the fact that a thin sheet of periosteum is more easily vascularized than is a segment of dense bone. With regard to free bone grafts, one cannot be sure that the new bone has not developed from elements of the endosteum or from the haversian system.

Costal fractures showed no tendency to heal if the fragments were separated from their periosteum by an interposed flap of muscle. The fragments became eburnated and partially absorbed. There was no evidence of callus from the endosteum, but there was a reaction in the fibrous tissue with consequent immobilization. New bone developed in the periosteal bed beneath the flap. These experiments indicate that the endosteum in the rib of the dog has feeble, if any, osteogenic properties and that the healing of the costal fractures is chiefly dependent on the presence of periosteum on the fragments.

In the experimental series it was seen that early rib regeneration hindered the progress of collapse with the multiple stage type of

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64. Phemister, D. B.: Necrotic Bone and the Subsequent Changes Which It Undergoes, *J. A. M. A.* **64**:211-216 (Jan. 16) 1915.

## CONCLUSIONS

1. Periosteum is definitely osteogenic and is a very important source of blood supply to bone.

2. Periosteum is the most important source of regeneration of bone and its presence is necessary for union in case of fracture.

3. The growth of osseous and periosteal transplants is in direct ratio to their ability to establish an adequate blood supply.

4. Solution of formaldehyde is superior to Zenker's solution as an inhibitor of costal regeneration, the inhibition which it produces lasting for at least four months.

The application of solution of formaldehyde U.S.P. diluted 1 to 10 to the periosteal beds in a series of clinical cases has not been accompanied by delayed healing of the wound or by any other disadvantage. No positive results can be stated as yet, because the series is small and the follow-up interval is too short.

The application of solution of formaldehyde to the periosteal beds is advocated in all resections of the ribs for the drainage of empyema or abscess of the lung. It is also advocated in first stage thoracoplasties, with the reservation that it should not be used in the bed of the first rib because of possible damage to the adjacent nerves and vessels by the formation of scar tissue.

5. The chemical inhibition of rib regeneration should not be employed in the Semb type of apicolysis, because in this operation the new bone aids in maintaining collapse of the lung.

from 14.3 per hundred thousand in 1931 to 11.5 in 1935, a decrease of 20 per cent. According to this same source, comparable data for the general population are available and show the same general downward trend.

It is not unlikely that this healthy trend is due to critical analysis of the situation by hospitals, medical societies and interested physicians. It is stated that because of self study and resulting educational propaganda Philadelphia has attained a death rate from appendicitis that is 81 per cent lower than the average of one hundred and seventeen other cities. When allowance is made for errors, this is shown to mean that Philadelphia has made a flat reduction of 75 per cent in its mortality from appendicitis.<sup>4</sup>

The New York Academy of Medicine has instituted a serious study of this problem and its Committee on Public Health Relations has been authorized to make a further study along the lines of the recent investigation of maternal welfare.

It is suggested that every surgeon and the staff of every hospital should prepare to answer the following questions:<sup>5</sup>

1. What mortality do you encounter from appendicitis?
2. In what percentage of cases is operation performed before rupture occurs?
3. In the cases in which rupture takes place, who is the cause of the delay: (a) the patient; (b) the family physician; (c) the surgeon?
4. Are cathartics responsible for the rupture?
5. If so, by whom were they administered: (a) the patient; (b) the patient's family; (c) the druggist; (d) the physician?
6. In the cases in which complications occur, has operation been immediate or deferred, and what mortality have you encountered in this special group of cases?

It is with the purpose of self analysis and of answering such questions as these in order to know where they stand on this problem that the staff of the Jameson Memorial Hospital, at New Castle, Pa., has undertaken a study of appendicitis. To gather material for this study it was decided to survey the records of all patients discharged from the hospital in 1935 and 1936 with a final diagnosis of appendicitis.

The total number of admissions to the hospital for this two year period was 5,943. The number of patients for whom a final diagnosis of appendicitis was recorded was 440 for the two years. Not allowing for readmissions or for the fact that some of the patients were not

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4. Foltz, J. A.: The Rising Mortality in Appendicitis and What We Are to Do About It, *J. Arkansas M. Soc.* 33:49 (Aug.) 1936.

5. Ramsdell, E. G.: Appendicitis: A Challenge, *New York State J. Med.* 35:673 (July 1) 1935.

The mass in the right side tended to subside. The temperature ranged between 101 and 104 F. and stayed at normal after the fifteenth day. Daily differential blood counts were made. On the nineteenth day the patient was discharged in good condition.

In the main the patients on whom no operation was performed were treated as follows: Nothing was given by mouth; ice bags were placed on the abdomen, and in some cases enemas were given. Frequent differential blood counts were made.

It is important to ask why operation was omitted in these cases, because it is the consensus of the hospital staff that operation is advisable when appendicitis presents itself. As has been seen, 1 patient was not operated on because age and cardiac decompensation rendered the prognosis unfavorable; a second because his condition was complicated by hemophilia, and a third, because she had diffuse peritonitis and was moribund (she died five hours after admission). Seven more patients were not subjected to surgical intervention because obviously they did not have appendicitis, although it was mentioned in the final diagnosis. Two probably had renal colic; 2 others had pain associated with the onset of menstruation; another 2, it seems probable from the records, had salpingitis. One patient apparently had gastroenteritis from infection caused by food. In 3 cases, in which the symptoms were mild and rapidly subsiding, diagnoses of subacute appendicitis were made and the patients were sent home after one day in the hospital. In 5 cases, with histories of repeated attacks of pain on the right side, diagnoses of chronic appendicitis were made. In 1 of these the patient returned to the hospital two months later and was submitted to operation.

Perhaps operation was not performed in the other cases of chronic appendicitis because the surgeons were acquainted with Bettman's study, made in 1928, which showed that of a series of 5,664 cases in which operation was performed for chronic appendicitis 40 per cent of the patients were unrelieved, 11.6 per cent were made worse and 1.7 per cent died. On the other hand, Charles Mayo pointed out that the day in which appendicitis was classified as of one of two types, the acute and the remunerative, is past. Dr. Mayo believes that there is a variable syndrome which is caused by chronic appendicitis. The problem is to recognize it preoperatively. Barber and Charles Mayo reviewed 100 cases in which they had performed exploration for certain unexplained abdominal symptoms after careful study. In these cases only the appendix was removed, and in each case it was reported to be chronically diseased. Five years later a check was made on the 100 patients. Sixty-nine said that they were cured, 21 that they were materially benefited and 9 that they were not helped. Although 2 of the 9 were better, they felt that the improvement was due to the removal of infected teeth and tonsils.<sup>6</sup>

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6. Mayo, C.: Appendicitis, *Southwestern Med.* 18:397 (Dec.) 1934.

61 and 70 and 0.5 per cent between 71 and 75. The youngest patient was 3 years old and the oldest 75. The ages of 8 patients were not recorded.

There were 60.2 per cent women and girls and 39.8 per cent men and boys in the group. However, when only the patients with simple acute appendicitis, with a suppurative, gangrenous or ruptured appendix are considered, excluding those in whom the appendix showed no pathologic condition, was chronically diseased or was subacutely inflamed, there were 99 men and boys and 90 girls and women afflicted, or 10 per cent more of the former.

The average time that elapsed from the onset of the acute attacks in this series until hospitalization was thirty-four and eight-tenths hours, or approximately one and one-half days. While in some of the cases the time elapsed appeared too long, the average is better than that reported by M. Reid and others from Cincinnati,<sup>7</sup> in whose series the average time that elapsed from onset to hospitalization was ninety-one and two-tenths hours. It is significant to note that in the cases of ruptured appendixes in the series reported from Jameson Hospital the average time that elapsed from the onset of illness to hospitalization was sixty-two and two-tenths hours, or two and one-half days, a period almost twice as long as the average elapsed time in all the cases of acute appendicitis considered together. In those cases in which an abscess had formed before the patients' admission to the hospital, an average of one hundred and eight hours, or four and one-half days, had elapsed from the onset of symptoms. Cutting down this interval is one of the ways by which the physician and the patient can attack the problem of complicated appendicitis.

Stanton<sup>8</sup> has shown after a study of 16,424 cases from the literature that when operation is done during the first twenty-four hours of the attack the mortality in experienced hands is almost negligible. When it is done during the first half of the second day the average mortality is from 2 to 3 per cent. For cases in which operation is done after about forty hours the rate tends to rise sharply, so that when the intervention is done on the third day of the attack the operative mortality averages about 10 per cent. In general, operations done on the fourth or the fifth day are even more dangerous than those done on the third day. Beginning with interventions on the sixth day, the operative mortality starts to decline, and when the operation is done on the ninth or tenth day the rate corresponds approximately with that for the second day.

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7. Reid, M. R.; Poer, D. H., and Merrell, P.: A Statistical Study of 2,921 Cases of Appendicitis, *J. A. M. A.* **106**:665 (Feb. 29) 1936.

8. Stanton, E. M.: Acute Appendicitis, *Surg., Gynec. & Obst.* **59**:738 (Nov.) 1934.

of the patients, among whom are included all those in whom the condition was acute and complicated. In the order of frequency the cathartics taken were: castor oil, liquid petrolatum, magnesia magma, magnesium sulfate, magnesium citrate, sal hepatica (a proprietary saline laxative) and mild mercurous chloride. In some instances the doctor who first saw the patient ordered the cathartic. Indeed medical practitioners should heed the present Reginald Fitz of Boston, who said: "Surely, in the early management of appendicitis to keep the bowels quiet should still be the first and last thought of the physician."<sup>9</sup>

The temperatures in the cases of simple acute appendicitis averaged 99.4 F., varying from 97.4 to 102.4 F. The pulse rates averaged 92, ranging from 74 to 122. The leukocyte counts averaged 9,435, varying between 6,450 and 27,900. The polymorphonuclear counts averaged 70.4 per cent, having a low of 56 and a high of 92.

In the cases of more serious involvement including instances of acute appendicitis with suppurative, gangrenous or ruptured appendixes, the temperatures averaged 101.8 F., with a range from 97 to 104.4 F., on admission. The pulse rates averaged 102, varying from 60 to 140. The leukocyte counts averaged 14,475, ranging from 8,100 to 24,650. The polymorphonuclear counts averaged 80 per cent, varying between 57 and 91.

Of the 396 cases in the series in which operation was done, the condition was acute in 189, as substantiated by pathologic diagnosis. Twenty-two of the cases were classified as instances of subacute involvement and 143 as cases of a chronic reaction, which means that infiltration of round cells and scarring or fibrosis had taken place in varying degrees as seen under the microscope. Forty-two appendixes were considered to be without pathologic manifestations. Thus, of the patients in this series, 48 per cent had acute appendicitis, 42 per cent had subacute or chronic appendicitis and 11 per cent had normal appendixes.

The cases of acute appendicitis may be subdivided as follows:

Simple acute .....	48, or 25%
Acute suppurative .....	86, or 46%
Acute gangrenous without rupture of appendix.....	20, or 11%
Acute gangrenous with rupture of appendix.....	30, or 19%

Among these cases of acute appendicitis, there were 11 instances of localized peritonitis, 12 instances of the formation of abscesses and 17 instances of spreading peritonitis.

There were 102 instances of discrepancy between the clinical and the microscopic diagnosis, that is, according to the pathologist, a 25 per cent error on the part of the surgeons. In 48 per cent of the cases in

9. Fitz, R.: On Perforating Inflammation of the Vermiform Appendix with Special Reference to Its Early Diagnosis and Treatment, *New England J. Med.* 213:245 (Aug. 8) 1935.



pital, 12 per cent had some degree of defect. A larger percentage of defects was noted in the cases in which approach was through a right rectus incision than in those in which a McBurney incision was used.

The stay in the hospital of the patients in the series ranged from four to one hundred and four days after operation, depending on such factors as the onset of complications, the use of drains and the initial severity of the condition. The average length of stay after operation was twelve and three-tenths days.

The following complications were present when the patients were admitted to the hospital or developed subsequently: There were 2 cases of pregnancy, in 1 of which abortion occurred on the fourth day after operation. There were complications of the chest in 6 cases (fibrinous pleurisy in 1, bronchopneumonia in 3, bilateral lobar pneumonia in 1 and empyema in 1). In 4 of these 6 cases the patients had received general anesthesia (nitrous oxide, oxygen and ether in 3 and nitrous oxide, oxygen and ethylene in 1), and in 2, spinal anesthesia (procaine hydrochloride). There was postoperative infection of the wound in 8 cases, pelvic abscess in 2, thrombophlebitis in 2, pyelitis in 1, cystitis in 1, fecal fistula in 1, pulmonary infarction in 1, otitis media of the left ear in 1, tonsillitis in 2, an abscessed tooth in 1 and infection of the upper part of the respiratory tract in 3. There were 13 patients whose temperature was above 101 F. later than the sixth day after operation, for reasons either not discovered or not recorded. Thus in 11 per cent of the cases in which operation was done there were complications of some sort caused by conditions other than the appendicitis.

Three hundred and seventy-seven patients received general anesthesia, usually with gas-oxygen induction followed by drop ether. A few were anesthetized by gas and oxygen alone or in conjunction with ether vapor. The gas was usually nitrous oxide, but ethylene was frequently used. One patient was given avertin (tribromethanol) supplemented by nitrous oxide and oxygen. Two patients were operated on under local anesthesia produced by procaine hydrochloride. Spinal anesthesia by procaine hydrochloride was used 16 times, or in only 4 per cent of the cases. No deaths attributable to anesthesia occurred.

In the two year period of 1935 and 1936, as has been pointed out, 440 patients were dismissed from the hospital with a diagnosis of appendicitis. The mortality for this whole group was 2.5 per cent. The mortality of 8.6 per cent which occurred in the group of 20 cases in which no operation was done has been discussed earlier in this paper. It was further noted that no deaths occurred among those patients whose appendectomies were only incidental to some other procedure. Of the 396 patients submitted to operation, 9 died, giving a mortality of 2.3 per cent for this group. This rate compares favorably with Davis'

There were more women with appendicitis than men, but a higher percentage of men had more serious forms of appendicitis.

The average time of thirty-four and eight-tenths hours from onset of symptoms to hospitalization is too long for the best management of appendicitis.

Too many persons go through first attacks of appendicitis without operative intervention.

Only 4 of every 10 patients presented histories typical of appendicitis.

Rectal examinations are important and should be recorded more frequently.

Too many patients receive cathartics for abdominal upsets which turn out to be appendicitis.

One fifth of the patients on whom operation was performed and two thirds of those who died had received cathartics, sometimes administered by the attending physician.

Approximately 5 of every 10 patients had acute appendicitis; 4 of every 10 had subacute or chronic appendicitis, and 1 of every 10 had a normal appendix.

Approximately 1 of every 5 patients whose condition was acute had a gangrenous appendix that had ruptured.

In approximately 1 of every 10 patients with acute involvement the condition was complicated with abscess or peritonitis.

The surgeon and the pathologist disagreed on diagnosis in 1 of every 4 cases.

The usual practice is to operate as soon as a diagnosis of acute appendicitis is made.

Incision is usually made through the right rectus muscle.

The stump of the appendix is inverted whenever this procedure is at all possible.

The average stay in the hospital is twelve and three-tenths days after operation.

In practically 1 out of every 10 cases the condition was complicated by something other than appendicitis.

Gas (nitrous oxide or ethylene), oxygen and drop ether are the usual anesthetics.

The mortality for the patients who were operated on was a small fraction over 2 of every 100.

The mortality for patients with acute gangrenous appendicitis with rupture was a fraction over 2 of every 10.

Death occurred in nearly 5 of every 10 patients with spreading peritonitis.

In view of this high mortality among patients with diffuse peritonitis, perhaps more attention should be given to the problem of devising some other plan of management for these patients. For example, operation might be deferred, as suggested by Arnheim and others.<sup>13</sup>

sloughing (Oderfeldt,<sup>11</sup> Capelle<sup>12</sup>); (8) incision in the wall of the intussusciens to permit manual reduction, followed by one of the aforementioned methods if necessary (Brown<sup>13</sup>). Statistics summarized from various clinics and from various individual reports show the appalling mortality of 70 per cent in 417 cases in which the patients were treated by one type or another of the foregoing operative procedures.

The optimal surgical technic for the treatment of irreducible or gangrenous intussusception occurring in early life should insure the following essential points: (1) rapidity of execution; (2) complete removal of the irreducible or gangrenous bowel; (3) control of the concomitant intestinal obstruction; (4) control of the loss of fluid, and (5) restoration of the continuity of the intestinal canal. Any discussion of these requirements in relation to the majority of the operative procedures outlined is outside the range of my experience. However, among 76 cases of intussusception in which the condition occurred in infants 2 years of age and under and in which the patients were treated in the surgical service of the Johns Hopkins Hospital there have been 6 instances in which resection has been indicated and performed. In all of the operations but 1, a resection of the ileum with end to end anastomosis, immediate resection followed by double enterostomy was the procedure of choice. Of the 6 patients, 3 died—a mortality of 50 per cent. It is the purpose of this paper to record my experience with the Mikulicz type of resection and to discuss in detail a modification in operative technic followed in the two most recent consecutive and successful resections.

#### REPORT OF CASES

CASE 1.—C. B., a white boy aged 10 months, was admitted to the Harriet Lane Home on Jan. 26, 1937, with a history of vomiting, abdominal pain and bloody stools. His illness had begun seventy-two hours previously. His birth, feeding and early development had been normal. He had had pertussis in April 1936 and had had frequent infections of the upper respiratory tract since that time, culminating in pneumonia and bilateral otitis media four weeks prior to this admission.

Seventy-two hours before admission the infant refused his afternoon feeding, and shortly thereafter he vomited. That evening he began to suffer from intermittent cramplike abdominal pain; it came on at hourly intervals and caused him to scream and clutch the side of his crib. He vomited throughout the night, and on the morning of the second day he was given an enema that returned with fecal material mixed with bright red blood. Attacks of pain and vomiting persisted, but they did not appear to be so frequent during the day as they had been

11. Oderfeldt, H., cited by Bickham, W. S.: *Operative Surgery*, Philadelphia, W. B. Saunders Company, 1924, p. 774.

12. Capelle, W.: *Vorschlag einer einfachen und radikalen Operationsmethode bei Darminvagination*, Deutsche Ztschr. f. Chir. **243**:745-748, 1934.

13. Brown, H. P., Jr.: *Acute Intussusception in Children*, Ann. Surg. **81**:637-645, 1925.

with a continuous suture of similar material. Four stay sutures of braided silk were laid. The fascial sheath was closed with interrupted figure-of-eight sutures of no. 0 chromic catgut. The edges of the skin were approximated with interrupted sutures of fine black silk.

*Postoperative Course.*—The child was given a transfusion immediately after the operation with 100 cc. of citrated blood, and a continuous intravenous "drip" of 5 per cent dextrose solution and 1.5 per cent saline solution was started. During the evening he vomited, and continuous gastric lavage was instituted. On the following day his condition rapidly improved, and the gastric siphonage was discontinued. On the third day after the operation water by mouth was given. This was followed by vomiting and by increasing abdominal distention, which became so alarming that the ileostomy was opened. Earlier in the day two stools had been passed by rectum. Relief from distention and from vomiting was immediate, and on the following day feeding by mouth was resumed. The parenteral intake of fluids was discontinued. During the next ten days the status quo was maintained, with drainage from the ileostomy and normal stools about equally divided in amount. The ends of the bowel could have been closed at any time, but this step was deferred because of the presence of an infection in the operative wound. Sixteen days after the operation bronchitis and bilateral otitis media developed. Loss of fluid through the ileostomy increased, the child's weight began to decrease, and his condition became progressively more critical. After twenty-four hours of parenteral intake of fluid the ends of the bowel were inverted with interrupted sutures of fine no. 1 catgut and the skin edges were approximated with silk sutures above the inverted bowel. The improvement after this procedure was dramatic, and the child was discharged on the twenty-eighth day after the operation.

*Pathologic Diagnosis.*—The diagnosis was ileocecal intussusception with necrosis of bowel.

CASE 2.—G. S., a white boy aged 7 months, was admitted to the Harriet Lane Home for Invalid Children on March 17, 1937. The admission note by Dr. William C. Stifler, Jr., of the resident staff, reads as follows: "The patient is a 7 month old white boy, who is admitted to the hospital because of vomiting and the passing of blood by rectum during the past thirty hours. The family history is non-contributory. The mother's labor was difficult, and the delivery of the child was by version and extraction. The neonatal period was normal. The feeding and the intake of vitamins have been fairly adequate. The development has been normal, and the baby has always been well except for a few colds, otitis media a few weeks ago and, since birth, a slight tendency toward constipation, for which he has been given castoria (an aqueous extract of senna with aromatics). Thirty hours before admission, at 6:30 a. m. yesterday, the child became ill very suddenly. He looked sick, whined as if in pain, vomited frequently and began passing by rectum material which apparently consisted of slime and blood, but no fecal material. He was given small amounts of milk and rather large amounts of water and continued to vomit. The vomiting has occurred two or three times every hour, has been unrelated to the milk and water taken by mouth, has been usually projectile, and has been watery and not stained green or brown. The baby has rested in bed very quietly, has whined and has had apparent attacks of pain, has slept little and has continued to look sicker and sicker. Today he has vomited every few minutes. There have been eleven passages of blood and slime by rectum, but no fecal material. No flatus has been observed. A physician was called yesterday morning and again later in the day. He attributed the

The baby was seen by the surgical consultant and an immediate laparotomy was advised. While the operating room was being prepared, the baby was given 150 cc. of a 5 per cent dextrose solution intravenously and specimens of his blood were grouped for transfusion.

*Operation.*—The operation consisted of the resection of a gangrenous intussusception and a double enterostomy, with lateral anastomosis.

With the child under anesthesia, obtained with ether by the drop method, the entire abdomen was prepared with a 3.5 per cent solution of iodine and a 70 per cent solution of alcohol and was draped in the usual manner. A long right rectus incision was made. When the peritoneum was opened, the intussusception was at once visible. It was a typical ileocecal intussusception, involving the entire large bowel to the rectosigmoid junction. Reduction was started by gently milking the mass from below and was successfully carried out until the last segment

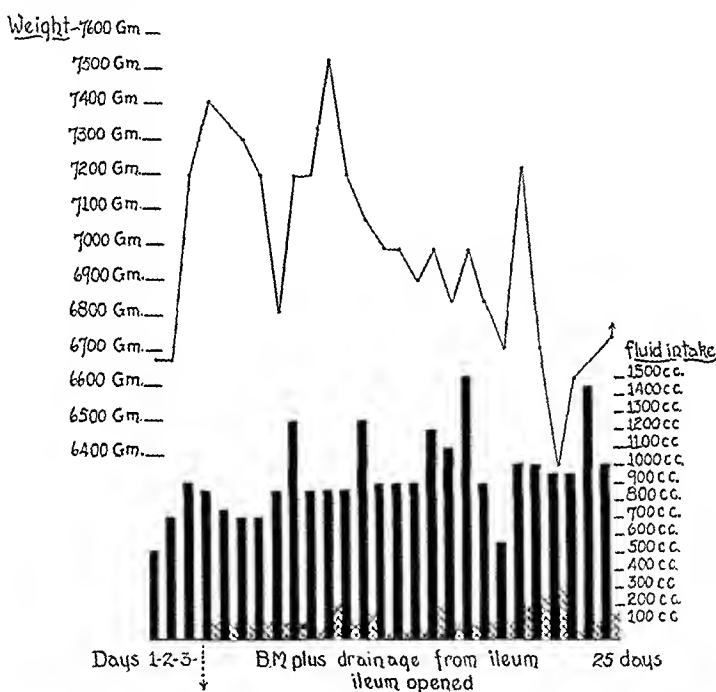


Fig. 2.—Early variation in fluid loss following resection with double enterostomy and failure to restore bowel continuity, recurrent over a period of nine months.

was reached. At this point even considerable pressure produced nothing but numerous rents in the serosa. The anterior wall of the intussusciens was incised longitudinally through the constricting ring, in the manner described by Brown. The mass was then forcibly reduced. The distal ileum was obviously gangrenous, and the necrotic area included a portion of the wall of the cecum and the appendix. The distal ileum at a point 10 cm. from the ileocecal valve was cut across with the actual cautery between crushing clamps. Its mesentery was clamped and divided. The peritoneum along the lateral abdominal wall was incised, and the cecum and the ascending colon were retracted mesially. There was an unusually long and mobile cecal mesentery. The mesenteric vessels to the large bowel were clamped and divided. The colon was resected between crushing clamps at a point just distal to the hepatic flexure. In addition to the gangrenous areas

immediate closure of the bowel ends and with the addition of lateral anastomosis. This modified Mikulicz resection has also been advised by Bier<sup>15</sup> in his *System of Surgery* for the treatment of sigmoid tumors. As far as can be ascertained, this modification of the Mikulicz resection has not been used previously in the radical treatment of gangrenous or irreducible intussusception in children.

From my experience with the successful operations recorded, this modification of the Mikulicz resection appears to fulfil adequately the requirements for the optimal surgical technic. It may not, of course,

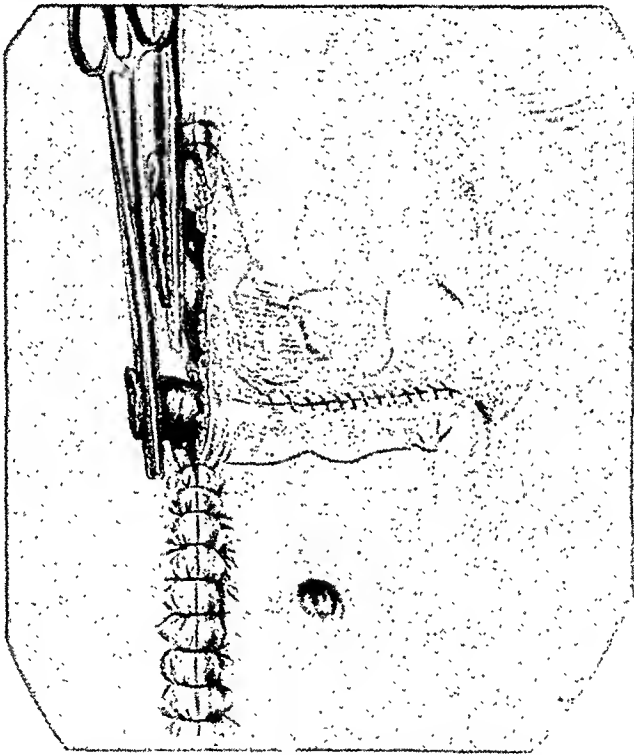


Fig. 3.—Simple operative technic of modified double enterostomy.

be applicable to all cases of irreducible or gangrenous intussusception, but it appears indicated in all but those of agonal character or those in which final reduction may be obtained by Brown's maneuver. Operative periods of thirty and forty minutes from incision to final dressing indicate that the lateral anastomosis adds little to the time consumed in the performance of a simple Mikulicz resection. Possible absorption from a "side-tracked" intussusception or from bowel left on the abdominal wall is of course eliminated by primary removal of the involved intestine.

15. Bier, A.; Braun, H., and Kümmell, H.: *Chirurgische Operationslehre*: II. Brustkorb und Bauch, Leipzig, J. Barth, 1912, p. 604.

# TOTAL BILE ACID-CHOLESTEROL RATIO IN HUMAN AND IN CANINE BILE

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The mechanism of the precipitation of cholesterol from bile to form gallstones has received increasing attention in recent years. Since the solubility of cholesterol in bile is dependent, to a great extent, on the presence of bile salts, considerable investigation has been directed toward the bile salt-cholesterol ratio in gallbladder bile. Experimental work on dogs clearly demonstrated that the wall of the inflamed gallbladder absorbs the bile salts of the contents rapidly, leaving an increased concentration of cholesterol.<sup>1</sup> A large number of studies of bile removed from the gallbladder either at operation<sup>1</sup> or at autopsy<sup>2</sup> in cases of disease of the bladder indicated that with the increasing inflammation of the organ the bile salt-cholesterol ratio was progressively lowered. This lowered ratio was obviously due to the decreased concentration of bile salts.

The methods employed by these various investigators for the determination of bile salts were either the Gregory-Pascoe procedure, which is specific for cholic acid only, or the Schmidt-Dart method, which measures only the conjugated bile acids. The investigations of

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1. (a) Rosenthal, F., and Licht, H.: Die Resorption der Gallensäuren in der normalen und entzündeten Gallenblase, *Klin. Wchnschr.* **7**:1952, 1928. (b) Andrews, E.; Schoenheimer, R., and Hrdina, L.: Chemical Factors and the Role of the Gall Bladder: Etiology of Gall Stones, *Arch. Surg.* **25**:796 (Oct.) 1932. (c) Johnston, C. G.; Ravdin, I. S.; Riegel, C., and Allison, C. L.: Studies on Gall Bladder Function: IX. The Anion-Cation Content of Bile from the Normal and Infected Gall Bladder, *J. Clin. Investigation* **12**:67, 1933. (d) Riegel, C.; Ravdin, I. S.; Johnston, C. G., and Morrison, P. J.: Studies of Gall Bladder Function: XIII. The Composition of Gall Bladder and Calculi in Gall Bladder Disease, *Surg., Gynec. & Obst.* **62**:933-936. (e) Reinhold, J. G.; Ferguson, L. K., and Hunsberger, A., Jr.: The Composition of Human Gall Bladder Bile and Its Relationship to Cholelithiasis, *J. Clin. Investigation* **16**:367, 1937.

2. Newman, C. E.: Beitrag zum Studium der Gallenniederschlags- und Gallensteinbildung, *Beitr. z. path. Anat. u. z. allg. Path.* **86**:187, 1931.

the cholic acid-cholesterol ratio (Gregory-Pascoe method) as well as the conjugated bile acid-cholesterol ratio (Schmidt-Dart method) was estimated.

#### PROCEDURE

The specimens of bile were obtained either from the gallbladder at operation (by aspiration) or from hepatic fistulas drained daily after the operation. In the latter cases the amount needed in making the determinations was taken from the whole twenty-four hour collection. The amounts of cholic acid, desoxycholic acid, total bile acids and conjugated bile acids were determined by a method previously described.<sup>7</sup> The amount of cholesterol was estimated by the method of Elman and Taussig.<sup>8</sup>

Two hundred and ninety-one analyses were made. These may be classified as follows according to the source of the bile examined.

##### A. Gallbladder Bile.

1. Bile collected from apparently normal human gallbladders. In addition to 3 specimens of bile obtained at operation, there were 2 specimens of "B" bile obtained by duodenal tube and 1 specimen obtained at autopsy immediately after death (6 analyses).
2. Gallbladder bile obtained in cases of carcinoma of the pancreas (13 analyses).
3. Gallbladder bile obtained at the time of operation in cases of chronic cholecystitis (diagnosis proved pathologically). The gallbladders were divided into two subgroups:
  - (a) Gallbladders visualized after the injection of tetraiodophenolphthalein (21 analyses).
  - (b) Gallbladders not visualized by means of tetraiodophenolphthalein (10 analyses).
4. Gallbladder bile obtained in cases of acute cholecystitis:
  - (a) Early acute cholecystitis (10 analyses).
  - (b) Hydrops of the gallbladder (7 analyses).
5. Gallbladder bile obtained in cases of pathologic conditions of the liver (8 analyses).

##### B. Bile Obtained Postoperatively from Fistula Drainage.

6. Hepatic bile obtained in cases of carcinoma of the pancreas (2 cases; 6 analyses) and of miliary tuberculosis (1 case; 2 analyses).
7. Hepatic bile obtained in cases of calculous cholecystitis associated with choledocholithiasis (13 cases; 39 analyses).
8. Hepatic bile obtained in cases of stricture of the choledochus, operation being performed eight months after the primary cholecystectomy (1 case; 7 analyses).
9. Hepatic bile obtained in cases of acute pancreatitis (3 cases; 16 analyses).
10. Hepatic bile obtained in cases of different types of hepatitis and cholangitis (8 cases; 42 analyses).
11. Hepatic bile obtained after administration of bile salts (2 cases; 46 analyses).

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8. Elman, R., and Taussig, J. B.: The Quantitative Determination of Cholesterol in Bile, *J. Lab. & Clin. Med.* 17:274, 1931.



(the early stage of "white bile"). The total bile acid-cholesterol ratio was 18.8, only a slight decrease from that in the first group. The average figure, then, for the total bile acid-cholesterol ratio is 21.6, agreeing closely with the figures given in table 1 for the bile acid-cholesterol ratio in bile from normal gallbladders.

*Gallbladder Bile Obtained in Cases of Chronic and Acute Cholecystitis.*—In the cases in which the gallbladder was visualized after the injection of tetraiodophenolphthalein, the average total bile acid-cholesterol ratio was found to be 13 (table 3). The fact that the dye could enter the gallbladder and be concentrated sufficiently for visuali-

TABLE 2.—*Gallbladder Bile Obtained in Cases of Carcinoma of the Pancreas with Obstruction*

Case	Choles- terol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio			
		Cholic Acid	Desoxy- cholic Acid	Total Bile Acids	Conju- gated Bile Acids	Cholic Acid	Desoxy- cholic Acid	Total Bile Acids	Conju- gated Bile Acids
Early obstruction:									
U.....	0.068	0.87	1.16	2.03	0.83	12.8	17.0	29.8	12.2
E. R.....	0.097	1.70	1.40	3.10	2.66 <sup>9</sup>	17.6	14.4	32.0	27.4
38.....	0.600	4.25	5.50	9.75	8.86	7.1	9.1	16.2	14.7
86.....	0.352	3.03	2.53	6.16	5.92	10.3	7.2	17.5	17.0
116.....	0.606	6.13	6.89	13.02	6.82	9.2	10.3	19.5	10.2
122.....	0.096	1.70	1.40	3.10	2.66	17.7	14.6	32.3	27.7
135.....	0.519	4.55	6.63	11.18	3.63	8.7	12.8	21.5	7.0
136.....	0.494	6.74	4.00	11.34	7.41	13.6	9.3	22.9	15.0
Average....	0.360	3.7	3.8	7.46	4.85	12.1	11.8	23.9	16.4
Advanced obstruction:									
55.....	0.008	0.03	0.11	0.14	0.12	10.0	36.6	46.6	40.0
127.....	0.008	0.015	0.11	0.125	0.15	1.9	13.7	15.6	28.7
137.....	0.026	0.09	0.02	0.11	0.19	3.5	0.8	4.3	7.3
141.....	0.106	0.26	0.22	0.48	0.57	2.4	2.1	4.5	5.4
144.....	0.074	0.95	0.37	1.32	1.00	13.0	5.0	18.0	13.5
Average....	0.040	0.27	0.17	0.43	0.40	6.2	12.6	18.8	17.0
Total average..	0.240	2.4	2.4	4.8	2.9	9.8	11.8	21.6	16.6

zation indicated that the gallbladder was functioning, that is, that it could fill and empty itself and could concentrate the bile fairly well. The cholesterol concentrations averaged 0.540 per cent. This is rather high when compared with the concentration of 0.360 per cent obtained in cases of early obstruction (table 2). The bile acid concentration, of 4.96 per cent, was lower than that which has been reported as normal.<sup>9</sup> An important question was raised: Had the bile acids been partially absorbed by the chronically inflamed gallbladder wall, or was the hepatic bile lower in bile acid concentration when it entered the gallbladder?

Bile obtained in cases in which the gallbladder was not visualized after the oral administration of dye (table 4) was found to have a total

9. Hammarsten, O.: A Text-Book of Physiological Chemistry, New York, J. Wiley & Sons, 1906, p. 275.

chronic cholecystitis. The figures for cholesterol gave an average of 0.546 per cent, and those for the total bile acids an average of 2.15 per cent. These figures seem to indicate that in acute cholecystitis the lowered bile acid concentration is due to a rapid selective absorption of bile acids, which leaves behind a relatively increased concentration of cholesterol.

TABLE 5.—*Gallbladder Bile Obtained in Cases of Acute Cholecystitis*

Case	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio			
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
34.....	0.080	0.14	0.34	0.48	1.15	1.7	4.2	5.9	14.4
35.....	0.105	0.12	0.33	1.05	0.99	1.1	3.8	9.9	9.4
81.....	0.877	0.73	1.39	2.12	1.26	0.8	1.6	2.4	1.4
90.....	0.789	1.25	7.09	8.34	7.03	1.6	9.0	10.6	8.9
111.....	0.506	0.18	0.12	0.30	0.03	0.3	0.2	0.5	0.03
120.....	0.470	0	0.30	0.30	0	0	1.0	0	0
123.....	0.126	0.57	1.35	1.95	0.76	4.5	10.9	15.4	6.0
180.....	0.135	0.36	0.91	1.27	0.69	2.3	5.8	8.1	4.4
143.....	1.625	0.08	0.61	0.99	0.64	0.04	0.5	0.54	0.4
151.....	0.750	1.58	3.05	4.63	5.58	2.1	4.1	6.2	7.4
Average.....	0.546	0.5	1.65	2.15	1.81	1.4	4.6	6.0	5.2

TABLE 6.—*Gallbladder Bile Obtained in Cases of Hydrops of the Gallbladder*

Case	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio			
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
66.....	0.016	0	0	0	0	0	0	0	0
82.....	0.012	0	0	0	0	0	0	0	0
119.....	0.500	0	0	0	0.52	0	0	0	1.0
121.....	0.272	0	0	0	0.23	0	0	0	0.8
122.....	0.063	0	0	0	0.34	0	0	0	5.4
149.....	0.003	0	0	0	0	0	0	0	0
150.....	0.067	0	0	0	0	0	0	0	0
Average.....	0.133	0	0	0	0.15	0	0	0	1.0

Table 6 presents the analyses made in 7 cases of hydrops of the gallbladder. These results apparently indicate that a fairly large concentration of cholesterol remains after the bile acids have been completely absorbed. The cholesterol content may be very high. Thus, in case 119 the cholesterol concentration was 0.500 per cent. A number of analyses of the protein content of the hydropic fluid indicated that high cholesterol content was usually associated with a high protein concentration. In cases in which the contents of the gallbladder were thin and watery, as in case 149, the cholesterol concentration was very low. Although neither cholic nor desoxycholic acid could be detected, analysis

patient suffering from jaundice and pruritus, operation revealed an enlarged congested liver but a normal gallbladder. A biopsy of tissue from the liver revealed a morphologically normal parenchyma, but the fine bile ducts contained precipitated pigment. Subsequent studies with iodized poppyseed oil showed the entire biliary tract to be extremely narrowed. This may have been the result of swelling of the surrounding parenchyma, a condition described by Eppinger under the term "serous hepatitis." In this case the total bile acid-cholesterol ratio was 38. In case 155 operation was performed immediately after an attack of severe pain and tenderness in the right upper quadrant of the abdomen, accompanied by high fever. At operation a thin-walled non-inflamed gallbladder containing stones was found. The liver was enlarged. The total bile acid-cholesterol ratio was 52.1. In both case 31 and case 40, a large atonic gallbladder containing thin bile was found.

TABLE 8.—*Hepatic Bile Obtained in Cases of Noncalculous Disease*

Case	Day After Operation	Choles-terol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio				Comment
			Cholic Acid	Desoxy- cholic Acid	Total Bile Acids	Conju- gated Bile Acids	Cholic Acid	Desoxy- cholic Acid	Total Bile Acids	Conju- gated Bile Acids	
57	15th	0.033	0.26	0.22	0.48	0.39	7.9	6.3	14.2	11.8	Carcinoma of pancreas
	17th	0.036	0.24	0.22	0.46	0.39	6.7	6.1	12.8	11.1	
121	2d	0.005	0.04	0.11	0.15	0	8.0	22.0	30.0	0	Carcinoma of pancreas
	3d	0.006	0.01	0.05	0.06	0.06	1.7	8.3	10.0	10.0	
	6th	0.016	0.03	0.07	0.10	0	0.8	4.4	6.2	0	
	20th	0.023	0.12	0.35	0.46	0.26	5.2	15.2	20.4	11.3	
52	15th	0.029	0.20	0.52	0.72	0.55	6.9	17.9	24.8	18.0	Miliary tuberculosis
	19th	0.020	0.14	0.72	0.86	0.46	7.0	36.0	43.0	23.0	

In these 2 cases biopsy of the liver showed considerable pericholangitic cellular infiltration and fibrosis. Both the cholesterol and the bile acid concentration were low, giving a ratio of 13.3 and 16.8 respectively. In case 46 operation was performed for sudden biliary obstruction due to acute pancreatitis. The gallbladder, containing thin bile, appeared normal. The total bile acid-cholesterol ratio was 56.6, owing to the very low concentration of cholesterol. These results suggest that when severe injury of the liver has occurred, as a result of inflammation, of degeneration or of acute obstruction, the cholesterol concentration of the gallbladder bile tends to be extremely low.

*Hepatic Bile Obtained in Cases of Noncalculous Disease.*—Three analyses were made in cases in which hepatic drainage was carried out for noncalculous disease (table 8). In case 57 and in case 121 drainage was done for carcinoma of the pancreas with obstruction. The patient in case 52, after an operation for acute pain in the right upper quadrant of the abdomen associated with high fever, was found to have miliary tuberculosis. In case 57 the total bile acid-cholesterol ratio was found

sented in some detail. Repeated intermittent biliary obstruction has been shown to lead to impairment of hepatic function, with a resultant low bile acid concentration of the hepatic bile even after prolonged drainage.<sup>4</sup> As a result, the total bile acid-cholesterol ratio in the cases considered here was low. In some instances there was a tendency for the ratio to rise gradually after the obstruction had been released. Certain exceptions must be noted. When operation was performed immediately during an acute obstruction (case of H. S. and case 28), the drainage bile during the first few days gave a very high ratio (88.1 for H. S. and 72.5 in case 28), apparently as a result of hepatic injury due to acute back pressure on the liver. One other point may be noted. In the case of S. M., after the administration of 4 Gm. of ox bile salts the total bile acid-cholesterol ratio rose from 8.12 to 30.9.

TABLE 10.—*Hepatic Bile Obtained in a Case of Stricture of Choledochus Eight Months After Operation (Case T. R.)*

Day After Operation	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio			
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
1st.....	0.037	0.05	0.05	0.10	0.10	1.3	1.3	2.7	2.7
3d.....	0.022	0.06	0.14	0.20	0.80	2.7	6.4	9.1	36.4
4th.....	0.039	0.08	0.17	0.25	0.94	2.0	4.4	6.4	2.4
5th.....	0.034	0.09	0.24	0.33	0.29	2.6	7.1	9.7	8.5
7th.....	0.030	0.08	0.32	0.40	0.17	2.7	10.7	13.3	5.7
9th.....	0.077	0.12	0.55	0.67	0.27	1.6	7.1	8.7	2.5
16th.....	0.100	0.08	1.23	1.31	0.37	0.8	12.3	13.1	1.7

*Hepatic Bile Obtained in Cases of Stricture of the Choledochus.*—A patient (T. R., table 10) had an almost complete obstruction of the choledochus for eight months as a result of a stricture following a primary cholecystectomy. The analyses revealed the excretion of the different bile acids to be in abnormal proportions. The predominant features were: (1) almost total absence of cholic acid, (2) a high proportion of desoxycholic acid and (3) a low concentration of conjugated bile acids. As can be seen, the total bile acid-cholesterol ratio was 2.7 on the first day, but thereafter it showed an average of about 10.

*Hepatic Bile Obtained in Cases of Acute Pancreatitis.*—The results of analysis of bile in 3 cases of acute pancreatitis are presented in table 11. In each instance the total bile acid concentration after about the eighth day tended to be much higher than in the previously presented cases of choledocholithiasis (table 9). The cholesterol concentration, however, also tended to be high. As a result the total bile acid-cholesterol ratio was rather low, except in the drainage bile on the twelfth day in case 62.

*Hepatic Bile Obtained in Cases of Hepatitis and Cholangitis.*—The analyses of hepatic bile made in 8 cases show the effect of injury to the liver on the excretion of cholesterol (table 12). The data can be correlated with the results of analyses of gallbladder bile obtained in cases of similar conditions (table 7). The high total bile acid-cholesterol ratio is especially to be noted in drainage bile obtained during the first few days in cases of hepatitis. In the case of F. F. the first two days' drainage gave a ratio of 275; in case 133 the ratio was 46.6 on the fourth day, and in the case of C. S. the ratio was 76.7 on the third day.

TABLE 13.—*Bile Obtained After Administration of Bile Salts in a Case of Complete Fistula Following Carcinoma of the Pancreas (case 23)*

Date	Choles- terol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio				Bile Acid Administered
		Cholic Acid	Desoxy- cholic Acid	Total Bile Acids	Conju- gated Bile Acids	Cholic Acid	Desoxy- cholic Acid	Total Bile Acids	Conju- gated Bile Acids	
Sept. 17	0.150	0.88	0.74	1.12	0.81	2.5	4.9	7.4	5.4	15 Gm. desoxy- cholic 10 Gm. desoxy- cholic 15 Gm. desoxy- cholic
18	0.129	0.47	0.61	1.08	0.96	3.6	4.7	8.3	7.5	
19	0.206	0.86	0.75	1.11	1.03	1.7	3.6	5.3	5.0	
20	0.173	0.25	1.19	1.44	1.42	1.4	6.9	8.3	8.2	
21	0.172	0.24	1.24	1.48	1.45	1.4	7.2	8.6	8.3	
22	0.121	0.13	1.66	1.79	1.82	1.1	13.7	14.8	15.0	
23	0.137	0.13	1.31	1.44	1.00	0.9	9.6	10.5	7.3	
24	0.128	0.70	0.38	1.08	0.92	5.5	3.0	8.5	7.2	
25	0.039	1.05	0.31	1.36	1.17	10.6	3.1	13.7	11.8	
26	0.077	0.89	0.62	1.51	1.25	11.5	8.0	19.5	16.6	
27	0.097	0.95	1.37	2.32	1.28	9.8	14.1	23.9	13.2	
28	0.112	0.95	1.13	2.18	1.11	8.5	10.1	18.6	10.0	
29	0.123	1.11	1.72	2.83	1.06	9.0	14.0	23.0	8.6	
30	0.112	1.07	1.34	2.41	0.95	9.6	11.0	20.6	8.5	
Oct. 1	0.149	0.71	0.44	1.15	0.56	4.8	3.0	7.8	3.8	
2	0.128	0.45	0.51	0.96	0.59	3.5	4.0	7.5	4.6	

In cases of chronic and acute cholangitis the total bile acid-cholesterol ratio tends to be rather low (cases of J. K. and F. J.). When both cholangitis and hepatic degeneration were found, the ratio tended to be low (case S. C.). On the other hand, when acute obstruction was associated with cholangitis (as in the case of J. K. after the eightieth day of drainage, and in the case of E. S.), the ratio was high. In 1 case (that of I. R.) bile drained through an edematous and inflamed gallbladder. As a result, a large proportion of the bile acids was absorbed, apparently much more rapidly than the cholesterol. This resulted in a very low total bile acid-cholesterol ratio.

*Bile Obtained to Determine the Effect of Administration of Bile Salts.*—In the case of S. M. (table 9) it was noted that the total bile acid-cholesterol ratio was raised following the administration of 4 Gm. of ox bile salts. Similar effects were produced in 2 other cases reported here. In case 23 (table 13) large amounts of desoxycholic acid and

took them for three day periods after he had completely recovered from the operation. Bile was collected over twenty-four hour periods, and equal quantities were pooled for three day periods. There was a daily loss of 300 to 500 cc. of bile through the fistula, but the loss of bile salts was partially made up by giving the patient 3 Gm. of ox bile salts every day. During the experimental period the cholesterol concentration gradually rose, but at the same time the bile acid concentration also rose, so that the total bile acid-cholesterol ratio did not vary with the different diets. The cholesterol concentration was highest during and after the taking of the fat diet, but the results, although suggestive, cannot be considered significant. It is of interest to note that after the

TABLE 15.—*Bile Obtained to Test the Effect of Various Diets on the Bile Acid-Cholesterol Ratio (Case of M. F.: Calculous Cholecystitis, Choledocholithiasis)*

Day After Operation	Cholesterol, %	Bile Acid Percentage			Bile Acid-Cholesterol Ratio			Diet for 3 Day Periods
		Cholic Acid	Desoxy-cholic Acid	Total Bile Acids	Cholic Acid	Desoxy-cholic Acid	Total Bile Acids	
20th.....	0.043	0.19	0.25	0.44	4.4	6.0	10.4	Hospital diet
22d, 23d, 24th..	0.073	0.21	0.18	0.39	3.0	2.5	5.5	High carbohydrate CHO, 700; P, 43; F, 3
25th, 26th, 27th	0.059	0.20	0.12	0.32	3.4	2.0	5.4	High protein CHO, 96; P, 244; F, 77
28th, 29th, 30th	0.111	0.36	0.27	0.63	3.2	2.4	5.6	High fat CHO, 18; P, 43; F, 300
31st, 32d, 33d...	0.148	0.55	0.27	0.82	3.7	1.8	5.5	Hospital diet
34th, 35th.....	0.121	0.38	0.31	0.69	3.1	2.5	5.6	Hospital diet
40th.....	0.095	0.56	0.40	0.96	5.9	4.1	10.0	Hospital diet; drainage after closure of tube for 5 days

fistula tube had been closed for five days, thus establishing a closed enterohepatic circulation of bile salts, the ratio rose to 10, and the bile acid concentration, although somewhat low, reached its highest point.

*Canine Gallbladder and Hepatic Bile.*—Since a great deal of investigative work has been done on canine bile, three tables are presented on the results of analyses of gallbladder bile and hepatic bile. Table 16 summarizes the results of 8 analyses of gallbladder bile. The average ratio was found to be 161 for cholic acid, 246 for total bile acids, and 135 for conjugated bile acids. Table 17 summarizes the results of analyses made during experiments on a dog with a McMaster fistula to which the bile was re-fed. The fistula was obstructed for a five day period and a ten day period by clamping the drainage tube. As can be seen, the total bile acid concentration tended to drop gradually after each period of obstruction. The cholesterol concentration tended to be

refed. The results are similar to those in the human being in that the concentration of cholesterol was not significantly influenced by increasing the concentration of bile acids in the bile as a result of their administration. Consequently the total bile acid-cholesterol ratio tended to be definitely increased each time bile salts were administered. It is to be noted that only a trace of cholesterol was present in the bile after the administration of dehydrocholic acid. This result may have been due to the fact that cholesterol is insoluble in dehydrocholic acid.

TABLE 18.—*Bile Obtained After Administration of Bile Salts to Dog with McMaster Fistula*

Dog 79: Day After Opera- tion	Choles- terol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio				Comment; Bile Acid Administration
		Cholic Acid	Desoxy- cholic Acid	Total Bile Acids	Conju- gated Bile Acids	Cholic Acid	Desoxy- cholic Acid	Total Bile Acids	Conju- gated Bile Acids	
4th	0.004	0.02	0.28	0.90	0.65	155	70	225	162	4 Gm. cholic (3 days)
8th	0.012	1.50	0.40	1.90	1.28	125	33	158	107	4 Gm. desoxy- cholic (3 days)
12th	0.013	1.82	1.31	3.13	0.68	140	100	240	52	8 Gm. desoxy- cholic (2 days)
16th	0.012	1.10	0.89	1.99	0.56	91	74	165	47	8 Gm. cholic (2 days)
20th	0.007	0.34	1.39	1.73	0.48	49	108	247	68	8 Gm. ox bile salts (2 days)
24th	0.006	0.56	1.14	1.70	0.30	93	190	283	50	8 Gm. glyco- cholic (2 days)
26th	0.008	0.36	1.75	2.11	0.30	45	218	253	37	8 Gm. glyco- cholic (2 days)
27th	0.010	1.01	1.72	2.73	0.98	101	172	273	98	8 Gm. cholic (2 days)
29th	0.010	1.34	1.65	2.99	0.35	134	165	299	35	8 Gm. ox bile salts (2 days)
31st	0.000	0.93	1.03	1.96	0.67	103	114	217	97	8 Gm. ox bile salts (2 days)
33d	0.011	1.64	1.91	3.55	1.50	149	173	322	136	8 Gm. ox bile salts (2 days)
34th	0.008	0.94	0.84	1.78	0.94	117	130	247	142	8 Gm. glyco- cholic (2 days)
36th	0.012	1.20	1.50	2.70	1.70	158	130	288	82	8 Gm. glyco- cholic (2 days)
38th	0.015	1.50	1.90	3.40	1.23	100	126	226	158	8 Gm. desoxy- cholic (2 days)
40th	0.012	1.90	1.52	3.42	1.90	158	126	284	60	8 Gm. desoxy- cholic (2 days)
43th	0.011	1.05	1.33	2.38	0.66	95	216	272	115	8 Gm. desoxy- cholic (2 days)
47th	0.012	1.05	1.33	2.38	0.66	95	216	272	115	8 Gm. desoxy- cholic (2 days)
49th	0.009	1.19	0.97	2.16	0.88	132	240	246	111	6 Gm. dehydro- cholic (2 days)
51st	0.008	0.37	1.00	1.37	0.89	147	125	272	200	
53d	0.004	0.58	0.41	0.99	0.56	102	247	246	140	
55th	0.001	0.22	0.71*	0.93	0.20	710*	930	200	520	
56th	0.001	0.33	0.50*	0.83	0.52	330	500*			

\* Dehydrocholic acid (?).

#### COMMENT

The data on gallbladder bile obtained from normal gallbladders and in cases of carcinoma of the pancreas as well as from hepatic drainage after the tenth day following the operation suggest that the normal total bile acid-cholesterol ratio in human bile lies somewhere around 20. In cases of early chronic cholecystitis the total bile acid-cholesterol ratio was found to average 13. With more advanced cholecystitis the ratio fell to 7.7 and when acute cholecystitis was present the ratio was 6. The

fully filtered, the desoxycholate-cholesterol ratio, 20, will be similar to that found by Spanner and Bauman<sup>5</sup> in a 3 per cent solution, and slightly lower in more concentrated solutions (table 19). If, however, sodium desoxycholate is dissolved in alcohol and excess cholesterol is added, addition compounds are formed. If this solution is dried, the residue redissolved in water and the excess cholesterol filtered off, the desoxycholate-cholesterol ratio will be found to be about 10. In other words, the danger of precipitation of cholesterol is no greater in a 1:80 solution of cholesterol in sodium cholate than in a 1:10 solution of cholesterol in sodium desoxycholate. In previous presentations<sup>4</sup> it was shown that with increasing degrees of cholecystitis the ratio of cholic acid to desoxycholic acid in the bile fell. Similar low ratios of cholic to desoxycholic acid were found in chronic cholangitis and also in prolonged intermittent biliary obstruction. It therefore follows that the total bile acid-cholesterol ratio is no indication of the degree of satura-

TABLE 19.—*Solubility of Cholesterol in Sodium Desoxycholate*

Percentage of Desoxycholate	Cholesterol Held in Solution After Mechanical Shaking		Cholesterol Held in Solution After Forming Addition Compound in Alcohol	
	Percentage	Ratio	Percentage	Ratio
2.0	0.085	23.5	0.156	12.8
4.0	0.240	16.6	0.400	10.0
5.0	0.476	16.8	0.770	10.4

tion of cholesterol in any one sample of bile. Since the amount of desoxycholic acid is relatively increased, a total bile acid-cholesterol ratio of 10 in bile from a patient with chronic cholecystitis may indicate a cholesterol saturation no greater than does a ratio of 20 in normal bile.

As a matter of fact, there are still unknown factors which keep cholesterol in solution in bile. The presence of phosphatides and of neutral fats and fatty acids in bile may exert a considerable influence in keeping cholesterol in solution. This is especially true of bile in which the bile acid concentration is very low. In such bile there may be a bile acid-cholesterol ratio as low as 1 (table 9).

The very high total bile acid-cholesterol ratio found in both the gallbladder bile and the hepatic bile of patients with hepatitis and with acute obstruction of the liver supports the conception, suggested by Wright and Whipple,<sup>10a</sup> that the excretion of cholesterol in bile is a

10. (a) Wright, A., and Whipple, G. H.: Bile Cholesterol: Fluctuations Due to Diet Factors, Bile Salt, Liver Injury, and Hemolysis, *J. Exper. Med.* **59**:407, 1934. (b) McMaster, P. D.: Studies on Total Bile, *ibid.* **40**:25, 1924. (c) Dostal, L. E., and Andrews, E.: Etiology of Gall Stones: III. Effect of Diet on the Bile Salt-Cholesterol Ratio, *Arch. Surg.* **26**:258 (Feb.) 1933. (d) Bac-



modify the excretion of bile cholesterol. The evidence recently presented by Dragstedt<sup>11</sup> that the pancreas secretes a hormone which is involved in the metabolism of fat is suggestive of a possible mode of attack on the problem.

If cholesterol tends to precipitate in bile in which the bile acid-cholesterol ratio is lowered, our evidence indicates that the ratio may be readily raised by the oral administration of bile salts. It is raised especially after the administration of cholic acid or of ox bile salts, which contain a high percentage of cholic acid. This seems to be due to the fact that in man the administration of cholic acid is more effective than the administration of desoxycholic acid in raising the concentration of bile acids in hepatic bile.<sup>12</sup>

#### CONCLUSIONS

The normal total bile acid-cholesterol ratio in human bile as determined in our studies was about 20. In cases of early chronic cholecystitis the ratio averaged 13, while in cases of advanced chronic cholecystitis the ratio averaged 7.7. The danger of the precipitation of cholesterol is only slightly increased, since the relative amount of the most effective solvent, desoxycholic acid, is greatly increased. In cases of acute cholecystitis the average total bile acid-cholesterol ratio was 6. The high cholesterol concentration increases the possibility of precipitation out of solution.

If the liver is injured, as in hepatitis, in inflammation or in acute obstruction, the excretion of cholesterol is much more markedly reduced than is the excretion of bile acids.

Evidence is presented which suggests that the excretion of biliary cholesterol is controlled by some independent function of the hepatic cell, which is related to lipid metabolism.

The bile acid-cholesterol ratio is readily raised by the oral administration of large amounts of bile salts, especially cholate. This may diminish the danger of the precipitation of cholesterol from the bile.

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11. Dragstedt, Z. R.; Van Poohaska, J., and Harms, H. P.: Observations on a Substance in Pancreas (Fat Metabolizing Hormone) Which Permits Survival and Prevents Liver Changes in Depancreatized Dogs. *Am. J. Physiol.* **117**:175, 1936.

12. Doubilet, H.: Hepatic Excretion in Man of the Various Bile Acids Following Their Oral Administrations, *Proc. Soc. Exper. Biol. & Med.* **36**:50, 1937.

quent finding was tenderness to palpation on the side on which the kidney was present; this occurred in 11 cases, or 16 per cent.

Cystoscopic observation of the trigon often will reveal signs suggestive of renal agenesis. Hypertrophy of the interureteral ridge on the side on which the kidney is present usually is well defined, and there is complete absence of the ridge on the other side. Compensatory hypertrophy of the ureteral orifice is usually evident, and urinary expulsion at this point is as a rule more energetic and frequent.

The average size of the normal kidney as measured by means of 100 consecutive excretory urograms was 12 by 6 cm. In 24 cases of renal agenesis the average size of the male kidney was 15.7 by 8.1 cm. and that of the female kidney was 14.8 by 7.1 cm. Thus, the long axis of the kidney averaged 0.9 cm. more for men than for women, and the width for men was 1 cm. greater than for women.

Measurements of the acquired solitary kidney were made with roentgenograms taken in 31 cases observed during the last six months. The average renal outline measured 14.7 by 7.1 cm. In the 8 instances in which the patients were women the average size was 14.6 by 6.6 cm. In the 23 instances in which the patients were men the average size was 14.7 by 7.2 cm. Thus, the chief difference was in the width of the renal outline. The degree of hypertrophy of the acquired single kidney is distinctly less than in cases of renal agenesis. These findings negate the opinion held by some surgeons that if a kidney on exploration is found to be normal and not hypertrophied there must be a functioning kidney on the other side.

There is a relative increase in size of the renal pelvis, which does not equal that of the parenchyma. Little difference in the size of the renal pelvis exists in cases of congenital or acquired single kidney. The renal outline generally is situated lower in cases of renal agenesis than in cases of acquired single kidney or normal kidney. This may be regarded as a definite factor in differential diagnosis. The outline of the psoas muscle is less sharply defined on the side on which the kidney is absent in urograms taken in cases of congenital and acquired single kidney than in an unselected series of urograms. In a few cases of agenesis there is an increase in the width of the psoas muscle on the side on which the kidney is absent.

Beer and Ferber<sup>2</sup> reported a series of cases of crossed renal ectopia (unilateral, fused or elongated kidney). Their report is in agreement with others previously published in that the left kidney was crossed more

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2. Beer, E., and Ferber, W. L. F.: Crossed Renal Ectopia (Unilateral, Fused or Elongated Kidney), with Report of Fourteen Cases Clinically Diagnosed and Two Cases Encountered at Autopsy During the Past Eighteen Years, *J. Urol.* 38:541-561 (Dec.) 1937.

referable to the displaced kidney. In 5 cases there were pressure symptoms but infection was not present.

The authors concluded that congenital displacement of the kidney is rare, occurring once in every 1,000 cases, although some types of this anomaly are seen more frequently than others. Infection, hydronephrosis and formation of calculus frequently are associated with this abnormality. Symptoms were present in all of Mackenzie and Hawthorne's cases, although they were not always considered urologic symptoms at the onset. Pelvic ectopia among women frequently occurs during pregnancy, and in such cases it can be dealt with by cesarean section before term. Elevation of the kidney, although at times successful, is usually a failure owing to the shortness of both the ureter and the renal pedicle.

Lower<sup>4</sup> stated that there are two types of cases in which one may be called on to treat the single diseased kidney: (1) cases of congenital absence of one kidney or congenital solitary kidney and (2) cases of acquired single kidney in which nephrectomy has been performed. With the first condition, congenital single kidney, there is no way of anticipating the disease. With the second condition, acquired single kidney, the possibility of subsequent disease may be anticipated by noting at the time of operation the pathologic changes in the kidney that is removed. In a series of 325 cases of nephrectomy the condition most frequently necessitating removal of a kidney was calculous pyonephrosis. Of the patients with this condition, 9.8 per cent had stone in the other kidney at the time of nephrectomy.

Tuberculosis was the condition for which the next largest series of nephrectomies was performed. Of the patients with this type of involvement, 12.36 per cent later had trouble with the remaining kidney, although tuberculosis could not be demonstrated at the time of the operation. The next series comprised cases of hydronephrosis; 10 per cent of the patients had trouble in the remaining kidney.

From the investigation of this series of cases and from his own experience in dealing with the diseased single kidney, Lower concluded that the first step should be one of conservatism. Although there is a large reserve in the kidneys under normal conditions, there is no reason why too much of this reserve should be sacrificed unless it becomes an absolute necessity. He suggested that conservative treatment in some cases would be better than a radical operation, especially when the lesion is likely to be bilateral. When the physician is confronted with a solitary diseased kidney, naturally there is only one procedure, that

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4. Lower, W. E.: *The Problem of the Single Diseased Kidney*. Tr. Am. A. Genito-Urin. Surgeons **30**:113-120. 1937.

exteriorization of its convex external border, compresses being placed about it to keep open the surgical incision of the walls. Stage 2 consists of nephrotomy performed by thermocautery, to drain out the pus and remove the calculi if they are mobile. If, however, they are ramified and coralliform and are adherent to the renal parenchyma, their removal is postponed and is performed as a third stage, twenty-four or forty-eight hours later.

Lithonephrotomy in two or three stages is indicated principally in cases of unilateral or bilateral calculus in which infection is severe, renal function deficient and medical treatment inefficacious. In such a case the patient becomes worse from day to day, possibly owing to pyonephrosis, uremia or glycosuria or to a poor cardiac condition. Unless an emergency arises the patient first should be put in the best possible condition; his resistance should be built up so that he can bear the operation satisfactorily, without suffering from shock. All the usual examinations and tests are carried out. Vaccination, especially auto-vaccination, prior to operation is an excellent measure to prevent septicemic complications. He should be fortified by injections of serum containing dextrose; the myocardium and the digestive system must be cared for meticulously as an indispensable part of the preparation. The least negligence in carrying out these details may cause disaster.

An illustrative case is reported in which the good results are attributed to performance of the operation in three stages, preceded by the building up of the patient's powers of resistance. The author stated that if he had used this technic in one of his early cases, to which he referred, operative shock and death of the patient would not have occurred. Experience in the treatment of 10 patients since that time, on all of whom he performed the operation in two or three stages, led him to report the details of his successful management.

One hundred and seventy-seven patients who had nephrolithiasis but who were not operated on at the time the diagnosis was established were observed by Priestley and Braasch<sup>8</sup> for an average of eleven years to determine their subsequent clinical course.

It was noted that: (1) Eighty-one and eight-tenths per cent of all unilateral stones and 97.8 per cent of all bilateral stones that were not removed surgically caused further symptoms referable to the urinary tract; (2) "silent" stones caused subsequent symptoms less frequently (66.66 per cent) than did stones which previously had caused pain (96.6 per cent); (3) large stones caused subsequent symptoms and necessitated later operation more frequently than did small stones; (4) stones in a calix caused subsequent trouble less often than did stones

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8. Priestley, J. T., and Braasch, W. F.: Late Results in the Conservative Management of Nephrolithiasis, *J. A. M. A.* **109**:1703-1705 (Nov. 20) 1937.

case of large renal tumor reported. Six of the tumors occurred in women and 2 in men. Four of the tumors were malignant.

The third unusual primary tumor of the kidney was a malignant transitional cell papilloma with local metastasis, arising in a loculus of an old hydronephrotic atrophic region in which there had been obstruction at the ureteropelvic junction owing to kinking, bands and adhesions. A malignant papilloma filled several of the loculi of the sac.

Hydronephrosis from obstruction of the renal pelvis by papillary tumors is frequent. No similar case of malignant papilloma arising in a loculus of an old hydronephrotic sac has been reported.

Bailey and Harrison<sup>10</sup> reported 5 cases of large benign renal neoplasm, discussing the pathologic picture and clinical behavior of the lesions. They stated that the problem of operative removal of large benign renal tumors is chiefly a question of correct approach. In 4 cases in this series, in which the tumor was removed by operation, the procedure was carried out by transperitoneal approach. In 1, removal was attempted through a lumbar incision but the renal pedicle was difficult to secure. The procedure was abandoned, therefore, and the tumor later was removed transperitoneally. The vascularity of the tumor, so strikingly demonstrated by the distended venous channels on its surface, is no longer a problem once the renal pedicle has been ligated.

Large dilated blood vessels on the surface of the tumor were present in all the cases. Bailey and Harrison emphasized this fact on account of the frequent presence of the same condition in association with malignant tumor of the kidney. Such a condition does not necessarily signify that the tumor has extended into the renal vein. It is reasonable to assume that the mere bulk of the new growth may so compress the renal vein as to cause dilatation of its collateral vessels. After the operation all 4 patients did well, and none of them had any recurrence of tumor.

The 4 patients were part (5.8 per cent) of a series of 68 patients on whom nephrectomy was performed for tumor. In view of the infrequency with which hypernephroma reaches such a size before operation is performed, the proportion of benign lesions among large renal neoplasms is even greater. Bailey and Harrison concluded, therefore, that patients who have large tumors and who give no evidence of metastasis always should be subjected to operative exploration.

Alcorn<sup>11</sup> reported a case in which a Wilms tumor occurred in an adult. He stated that Kilbane and Lester in 1929 found only 15 such

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10. Bailey, O. T., and Harrison, J. H.: Large Benign Renal Neoplasms: Their Pathology and Clinical Behavior, with Report of Five Cases, *J. Urol.* **38**: 509-529 (Dec.) 1937.

11. Alcorn, K. A.: Wilms' Tumor in an Adult: Report of a Case, *Proc. Staff Meet., Mayo Clin.* **12**:692-694 (Nov. 3) 1937.

Higgins<sup>13</sup> reported the cases of 5 patients who had squamous cell carcinoma of the renal pelvis, seen at the Cleveland Clinic. Including the records of their cases, the literature now contains 64 reports of squamous cell carcinoma of the renal pelvis.

The relation between leukoplakia and squamous cell carcinoma of the renal pelvis frequently is cited in the literature. The striking relation between renal calculi and squamous cell carcinoma has been noted by many observers. It has been stated by some authors that the development of such metaplastic changes may be induced by long-continued irritation due to chronic inflammation of renal calculi. This seems especially probable, because a review of a number of reports of cases indicates that the presence of chronic inflammation of the renal pelvis or calculi seems definitely to antedate the presence of the malignant lesion.

No symptoms are definitely pathognomonic of squamous cell carcinoma of the renal pelvis. Each of Higgins' patients complained of symptoms referable to pyuria due either to a calculus or to chronic inflammation. They also complained of pain in the back. The latter symptom has been present in 43 per cent of cases in the collected series. Loss of weight is a late manifestation, usually occurring after metastasis has taken place.

Two types of lesions predominate: In the first type the cells early invade the renal parenchyma and eventually replace it. The second type of lesion is confined chiefly to the renal pelvis; the region is covered with tumor which in some areas has a papillary appearance. With this type, involvement of the ureteropelvic junction occurs earlier, and a severe degree of hydronephrosis, with atrophy of the renal parenchyma, is found.

Early diagnosis followed by nephrectomy is the procedure of choice. In Higgins' series, in which high voltage roentgen therapy was employed preoperatively, there was no evidence of reduction in the size of the tumor. Postoperative roentgen therapy is advisable.

The prognosis is grave because of the frequency of metastasis. In a review of the literature, Higgins was unable to find the report of a patient who was free from metastasis at the end of five years.

Patch<sup>14</sup> reported 9 cases of tumor of the pelvis and ureter. Six of the tumors were in the pelvis, 2 being benign papilloma, 1 malignant papilloma, 2 squamous cell carcinoma (in 1 case associated with leukoplakia) and 1 transitional cell carcinoma.

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13. Higgins, C. C.: Squamous Cell Carcinoma of the Kidney Pelvis, *Tr. Am. A. Genito-Urin. Surgeons* 30:13-33, 1937.

14. Patch, F. S., in discussion on Caulk, J. R.: Tumors of the Renal Pelvis and Ureter, *Tr. Am. A. Genito-Urin. Surgeons* 30:71-73, 1937.

Conclusions were based on a study of 46 of the 71 cases, 25 being excluded for the following reasons: In 8 cases there was not satisfactory evidence in regard to the conditions at reasonable periods after the operation; 2 patients died, and in 15 cases nephrectomy was done.

The types of operation were as follows: (1) resection of the renal pelvis (21 cases); (2) resection with reimplantation of the ureter (9 cases); (3) reimplantation of the ureter (3 cases); (4) division of one or more abnormal vessels to the lower pole (2 cases); (5) ureterolysis (2 cases); (6) ureteropyeloneostomy (4 cases); (7) miscellaneous procedures (5 cases), and (8) nephropexy combined with various of the procedures mentioned (19 cases).

Nephrostomy alone was employed in 5 cases. Nephrostomy as an adjunct to various plastic operations was employed in 48 cases.

Secondary nephrectomy was required in 15 cases, or 21.12 per cent. It does not appear that these unfavorable results were associated with any particular type of operation. Thus, in 9 of the cases resection was performed, whereas in each of the remaining 6 cases a different type of operation was done. It will be noted that 12 of the 15 patients were treated by nephrectomy within the first year; 1 two and a half years later, and 2, seven years later.

With the exclusion of certain cases for various reasons, Walters, Cabot and Priestley<sup>16</sup> had 46 cases on which to base their report on operative results in cases of hydronephrosis; reports were made on the basis of pyelographic evidence (26 cases) and also on the basis of reports by letter (20 cases). They have not considered as conclusive any pyelographic evidence which was obtained less than seven months after operation. The group of cases in which reported results were based on pyelographic evidence includes, therefore, cases in which pyelographic studies were done from seven months to more than seven years after the operation.

Considering first all of the various types of operations together, they have classified on pyelographic evidence the results in 5 cases as excellent and in 8 as good; in 5 others the condition of the patients was classified as improved, and in 8 others as not improved. Of the remaining cases, classified on the evidence of letters, in 7 the results have been classified as good; in 8 others the condition of the patients was classified as improved, and in 5 others as not improved. The total results, from evidence both of the pyelogram and of the letters, are as follows: in 5 cases, excellent; in 15, good; in 13, condition improved; and in 13, condition not improved. In a word, 33 of the 46 patients (71.7 per cent) have benefited definitely by the operation, and 13 have not.

Judged by the aforementioned criteria, the results for patients for whom the operation was classified as "resection of the renal pelvis" (21 patients) indicate that of 9 for whom the reported results were based

terior surfaces for a distance of 2 or 2.5 cm., and after its insertion into its new mouth at the most dependent portion of the renal pelvis the straps of the ureter are drawn outward laterally from the pelvis through two small stab wounds on either side of the new neostomy, and a mattress suture is employed to fix them in position. The knots are placed outside the renal pelvis. From this point on, Papin's method of transrenal drainage and resection of the redundant pelvis is carried out. Both the Garoeau catheter that serves as a splint for the new anastomosis and the Pezzer catheter that drains the kidney are brought out through the same nephrostomy wound. Nephropexy is employed if the kidney has been mobilized.

Work on 4 experimental subjects with this method has proved gratifying. The experimental stage has been divided into two separate periods, the work during first period being limited to the ligation of the ureter and the formation of hydronephrosis. The ligature about the ureter was tied 2.5 cm. from its renal insertion, by means of silk threads.

A period of two to five months was allowed to elapse before the second stage (plastic repair) was performed. All experimental subjects survived. The tests for renal function, as performed by the insertion of the Pezzer catheter, showed return of function in a very short time after plastic repair.

Hepler<sup>19</sup> stated that from the etiologic standpoint dilatation of the upper part of the urinary tract, occurring in children, may be divided into three types: (1) that due to mechanical obstruction, most frequently to congenital fibrosis, muscular hypertrophy or exaggerated constriction at the points of normal anatomic narrowing, that is, the ureteropelvic and ureterovesical junctions and the vesical outlet; (2) that occurring as a sequela of a neural condition, either central or peripheral, involving the bladder (such as poliomyelitis, cerebrospinal syphilis, spina bifida, toxic neuritis or the less definite dysfunctions classified as idiopathic); and (3) that for which no obvious cause, either mechanical or dynamic, can be demonstrated.

Hepler<sup>19</sup> discussed functional imbalances at the ureterovesical junction as a possible cause in some cases of dilatation of the third type.

The lower and intramural part of the ureter and the vesical trigon may be considered an anatomic and physiologic unit. These structures have a common embryologic origin which is distinct from that of the rest of the bladder. The muscles of the trigon are formed from a continuation of the longitudinal fibers of the ureters, the lateral extensions forming Bell's muscle and the mesial extensions, which unite with

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19. Hepler, A. B.: Nonobstructive Dilatations of Upper Urinary Tract in Children. *J. A. M. A.* **109**:1602-1606 (Nov. 13) 1937.



mechanisms of the two conditions are similar. The indications for treatment of a condition which is so little understood and concerning which there have been so few clinical data are not clearly defined. The following methods have been advocated: (1) presacral neurectomy; (2) plastic resection of the ureterovesical junction; (3) incision of the junction by high frequency current, and (4) gradual dilation for high degrees of obstruction.

Foley<sup>20</sup> described a new plastic operation for stricture at the ureteropelvic junction. A large incision which provides adequate exposure and complete freeing of the kidney is essential. By careful examination the exact anatomic relations responsible for obstruction are determined. Adhesions between the pelvis and the ureter are severed completely, which accurately exposes the ureteropelvic junction. The latter is examined carefully by inspection, by palpation and, if necessary, by instrumental exploration through a small pyelotomy. By these means the presence or absence of "stricture" is determined and the question of the need for plastic operation is answered.

The kidney and ureter are held in position to give facility in accurately placing the Y incision in the pelvis and ureter. The stem of the Y is placed in the lateral wall of the ureter and thus will face the pelvis when normal position is restored. The incision is carried through the ureteropelvic junction and downward in the medial wall of the pelvis for an appropriate distance below the ureteropelvic junction. From this point the incision continues as two diverging limbs in the lower medial wall of the pelvis, in the form of an inverted V. The incision in the ureter should equal in length the incision in the pelvis plus the length of the V-shaped flap. The triangular opening in the pelvis and the triangular flap of pelvic wall when turned down face directly the incision in the ureter.

The apex of the flap approximates directly the lower angle of the ureteral incision. By closely spaced interrupted sutures of 0000 chromic catgut embracing only the muscularis (with careful avoidance of the mucosa) the edges of the ureteral incision and the edges of the triangular defect in the pelvis are approximated directly, the tip of the flap fitting neatly into the lower end of the ureteral incision.

When the suturing is completed a soft rubber catheter of size 10 or 12 French is introduced through a small stab opening on the posterior surface of the pelvis and is directed into the ureter for a distance of 6 or 8 cm. A number of small fenestrations are cut in the portion of catheter that is to lie within the pelvis. The catheter serves as a splint for the sutured segment and provides for drainage of urine from the

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20. Foley, F. E. B.: A New Plastic Operation for Stricture at the Uretero-Pelvic Junction: Report of Twenty Operations, *J. Urol.* **38**:643-672 (Dec.) 1937.

underlying pathologic condition. If this can be accomplished, the hydronephrotic kidney will be found in many instances to retain a respectable amount of function and will cause no symptoms, although its pelvis may seem grossly abnormal on pyelographic examination. Unconquerable infection, however, will spoil all surgical efforts. Nephrectomy, when possible, is then the only relief.

Kafka<sup>22</sup> reported the case of a girl aged 4 months who had congenital hydronephrosis on the left side. The condition was so advanced that the kidney was a unilocular cyst with a thin wall of renal parenchyma. Hydronephrosis resulted from atresia of the ureter, which began at the pelvis and extended downward, making a diverticular pouch about 1 cm. in length. Nephrectomy was performed, and the child recovered. At the same time there was congenital dislocation of the right hip, for which operation was performed a year later. Six years later the child was in excellent condition.

Crabtree<sup>23</sup> stated that pregnancy does not alter the position of the kidneys. If the renal shadow gives evidence of an abnormal relation to other organs, the condition is generally due to anomalies antedating pregnancy. Abnormalities of the calices, pelvis and the ureter may be attributable to pregnancy, but rounded calices have not the same significance when they occur in pregnant women as when they occur in patients who are not pregnant. Congenital abnormalities of the pelvis and ureter and preexisting alterations caused by disease generally are recognizable in cases of pelvic dilatation due to pregnancy, as pregnancy may exaggerate previously existing conditions.

When intravenous pyelographic examination shows the lower two thirds of the ureter completely filled, the condition should be considered pathologic. There is sufficient evidence to reestablish the fact that relaxation of the muscles of the renal tree associated with pregnancy may be due to the effects of pregnancy on the endocrine glands.

The excretion of drugs used for intravenous pyelographic examination is apparently retarded by pregnancy both of women and of experimental animals. Decreased motility in cases of large pelvic and ureteral dilatations interferes with diffusion of the excreted dye and thus produces a less satisfactory demonstration of the pelvis and ureter.

The essential differences between a chronic obstructive lesion and an obstructive lesion which has its origin in pregnancy must be recognized. The former is characterized by hypertrophy of the muscles, decompensation after the limit of hypertrophy has been reached and changes due to fixation, which limit indefinite dilatation.

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22. Kafka, V., Jr.: Ein Fall von Hydronephrose bei einem 4 Monate alten Säugling bei gleichzeitigem Bestehen einer Hüftgelenksluxation, *Ztschr. f. Urol.* **31**:602-606 (Sept.) 1937.

23. Crabtree, E. G.: Hydronephrosis of Pregnancy, *J. Urol.* **38**:605-619 (Dec.) 1937.

Congenital hydronephrosis unassociated with other anomalies of the urinary apparatus exists as a distinct clinical entity and is probably far more frequent than is conceded in the literature. Associated stones are caused by pre-existing stasis; accessory vessels and ptosis play a minor role and are factors only in the late stages of the development of hydronephrosis. Valve formation or high insertion of the ureter is a result of pelvic dilatation rather than its cause. Hydronephrosis frequently accompanies a malformation of the kidney or ureter, such as bifid and double pelvis and ureter, fused, ectopic and horseshoe kidney, aberrant distribution of blood vessels or congenital structure and valve formation of the ureteropelvic junction. With such conditions hydronephrosis may accompany the renal anomaly at birth; or poor drainage resulting from malformation may produce hydronephrosis later in life, superimposed infection playing an important role.

Acquired hydronephrosis resulting from mechanical obstruction at the ureteropelvic junction or the upper part of the ureter long has been recognized. In a great number of cases of hydronephrosis the condition is so caused. Of interest is the dynamic type of hydronephrosis due to neuromuscular dysfunction either associated or not associated with pyelonephritis.

Traumatic hydronephrosis is a clinical entity. It is usually the result of late sequelae of, and is occasionally the immediate result of, direct or indirect trauma to the kidney. Obstruction is produced by strangulation of the ureter due to cicatricial changes resulting from organization following extravasation of blood and urine in the perinephrium. In rare instances hydronephrosis is due to obstruction from blood clots, sudden displacement of the kidney or dislodgment of pre-existing renal calculi.

*Tuberculosis.*—Mathé<sup>26</sup> has observed 6 cases of unilateral renal tuberculosis in which the condition occurred in children and adolescents aged 2, 10, 13, 16, 17 and 18 years, respectively. Four patients are living and in good health ten, eight, three and two years after operation, respectively. Two died six months and five years, respectively, after operation as the result of generalized spread of the disease.

In reviewing 4,698 cases of unilateral renal tuberculosis, Mathé found that this disease was present in 565 patients (12 per cent) between the ages of 1 and 20 years; there were 20 occurrences (0.42 per cent) in children from 1 to 5 years of age; 51 occurrences (1.08 per cent) in children from 5 to 10 years of age, and 494 occurrences (10.5 per cent) in adolescents between 10 and 20 years of age. The statistics

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26. Mathé, C. P.: La tuberculose rénales de l'enfant, Arch. d. mal. d. reins 10:517-544 (Nov.) 1936.

One girl, aged 15 years, had a functionless kidney with practically no symptoms. Three young women had borne children; 1 had pyelitis while pregnant.

In a series of 200 cases of chronic pyelonephritis recently observed at the Mayo Clinic by Braasch,<sup>28</sup> bacilli of the colon group were found in 110 cases. *Escherichia coli* was present in 84 cases, or 42 per cent, and *Aerobacter aerogenes* in 26 cases, or 13 per cent.

Next in frequency, cocci are found in the urine in cases of chronic pyelonephritis. In the series of 200 cases they were found in 28, or 14 per cent. Their presence is noted often on microscopic examination of the urinary sediment when cultures are sterile. Some bacteriologists regard them not as etiologic factors but as unimportant secondary invaders and as being frequently the result of contamination.

Streptococci are found only occasionally in the voided urine in cases of chronic pyelonephritis and less frequently when the urine is catheterized. In the series of 200 cases of pyelonephritis they were present in only 8 cases, or 4 per cent.

*Proteus* was found to be the infecting organism in only 6 cases, or 3 per cent. This organism is not satisfied with being an indolent invader causing chronic infection; either it exercises its destructive activities so as to destroy the kidney with diffuse purulent infection or malignant formation of stones, or it disappears after a short period of infection.

In the series, bacterial pyuria was found in 44 instances, or 22 per cent. It was observed most frequently in cases of advanced renal infection of long standing accompanied by cicatricial changes or by impaired renal function.

A review of the 200 cases showed that the  $p_H$  of the urine, with but few exceptions, fell in the neutral zone, between 5.9 and 6.5.

A complication which frequently is observed in association with chronic renal infection is that of secondary formation of stone. In a series of 526 cases of chronic bilateral pyelonephritis observed at the clinic in the past seven years, secondary lithiasis was found in 28. Lithiasis secondary to chronic pyelonephritis is often bilateral, as is shown by the fact that stones were found in both kidneys in 9 cases of this group of 28, or 32 per cent. When bilateral the stones usually are multiple. Unilateral stones were found in 19 cases; they were single in all but 4. When there is chronic bilateral pyelonephritis and a stone is present in one kidney the renal infection usually is primary, because infection which occurs secondary to stone seldom is transmitted to the other kidney.

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28. Braasch, W. F.: Clinical Data Concerning Chronic Pyelonephritis, *J. Urol.* 39:1-25 (Jan.) 1938.

tion of the calices. Adynamic or atonic ureterectasis may be explained by periureteritis affecting the trophic nerves which supply the ureteral wall.

Surgical treatment, the need for which is surprisingly infrequent in these cases, usually is not indicated unless one of the following conditions is present: some form of obstruction; localized, persistent infection; destruction of renal function; or atrophy. Such treatment was found necessary in only 3 per cent of the 526 cases of chronic pyelonephritis observed by Braasch<sup>28</sup> at the Mayo Clinic in the past seven years.

In the recent developments of chemotherapy, compounds have been produced which have given startling results: sulfanilamide and mandelic acid. Although sulfanilamide gives promise of being a potent factor in eradicating renal infection in many cases, in common with other similar drugs it is of greater value against acute than against chronic infection. There is a vast difference in the results obtained in treatment of chronic and of recent renal infection. Although most renal infections when acute, subacute or recurrent can be controlled by recently developed chemotherapy, the secondary and anatomic changes associated with chronic infection often will defy all treatment.

Eradication of chronic pyelonephritis is possible by prophylaxis and by thorough, intelligent treatment of acute and subacute infection. Treatment of urinary infection still demands the intelligent supervision of the urologist.

In 2 cases in which the patients were men reported by Albright, Dienes and Sulkowitch,<sup>29</sup> roentgenograms of the kidneys showed multiple deposits of calcium in the pyramids. The deposits were larger and of less uniform size than those seen in cases of nephrocalcinosis associated with hyperparathyroidism. Small gram-negative bacilli were present in the urine of both patients; the organism was identified as *Haemophilus influenzae*. The urine of both patients was constantly alkaline, probably owing to the property of *H. influenzae* to split ammonia from urea, and the deposits of calcium were presumably attributable to the alkalinity so produced. Sulfanilamide promptly eliminated *H. influenzae* from the urine, with resulting acidity of the urine.

*Parenchymal Infection.*—Hamer<sup>30</sup> stated that metastatic renal infection includes a group of lesions of the kidney, due to blood-borne infection, with which there is no urogenital abnormality acting as an accessory cause. The source of the infection is usually some remote peripheral focus, such as a carbuncle, a boil, an infected wound or an

29. Albright, F.; Dienes, L., and Sulkowitch, H. W.: Pyelonephritis with Nephrocalcinosis Caused by *Haemophilus Influenzae* and Alleviated by Sulfanilamide: Report of Two Cases, *J. A. M. A.* **110**:357-360 (Jan. 29) 1938.

30. Hamer, H. G.: Diagnosis and Treatment of Metastatic Renal Infection, *J. Urol.* **38**:530-540 (Dec.) 1937.

in which circulation to the kidney was obstructed for over ninety minutes the kidney was destroyed completely.

Westerborn concluded that the same conditions prevail in man and that it may be possible to preserve a human kidney obstructed by embolus, but only if the embolus can be removed within possibly the first hour after obstruction. This time might be extended if the obstruction is not complete. The obstruction probably was not complete in Westerborn's case, in which the crushing of the embolus forty-eight hours after obstruction reestablished temporary renal function.

*Pelvic Pain.*—The renal pelvis varies so markedly within normal limits that it is difficult to set any normal standards. Notwithstanding this fact, Minder<sup>32</sup> concluded that there is a definite connection between infection, pain and the form of the pelvis. The fact that a renal pelvis is anatomically normal is not proof that its function will be normal. A disturbance of urinary excretion may cause the same amount and type of trouble as are caused by morphologic changes of the renal pelvis. The position of the kidney is of little importance in relation to the situation of pain. Abnormality of the ureteropelvic junction together with infection increases the incidence of pain in the case of any diseased kidney. A low or ptotic kidney should not by itself cause pain.

*Renocolic Fistula.*—Wesson<sup>33</sup> stated that renocolic fistulas occur secondary to a chronic suppurative renal lesion associated with perinephritis or perinephric abscess. He reported cases; the fourth patient, aged 87, died before any diagnostic procedures could be carried out. In 1 case the fistula passed directly from the bowel through the substance of the kidney to a calix. In the other 2 the opening was in the pelvis and was connected indirectly, through a perinephric abscess, with the bowel. In 1 case the fistula developed nine years before the operation, and the patient's good health during the interim was attributed to the treatment of a nonexistent cancer by means of roentgen therapy. A silent renal staghorn calculus was present in 1 case, but the fistula was caused by a proteus infection.

The morbidity and mortality rate from proteus infection in the genitourinary tract is very high.

*Observations on the Capsule.*—Rolnick<sup>34</sup> stated that the true capsule acts as a protective barrier to trauma and prevents the spread of infection to the kidney. There is a constant interchange of fluid on the renal surface, which may be of considerable clinical and physiologic

32. Minder, J.: Ueber den Zusammenhang zwischen Nierenschmerz, Beckenform und Infektion, *Ztschr. f. Urol.* **31**:586-595 (Sept.) 1937.

33. Wesson, M. B.: Renocolic Fistulae: Reports of Three Cases, *Tr. Am. A. Genito-Urin. Surgeons* **30**:159-167, 1937.

34. Rolnick, H. C.: Some Observations on the Renal Capsule, *J. Urol.* **38**: 421-426 (Nov.) 1937.

always wide in extent and was diffused beyond the region of the incision. Moreover, the degenerative processes within the cortex were much more advanced than in tissues incised with the scalpel and consisted of changes which involved indifferently the tubules and the glomeruli. Thus, de Vincentiis concluded that the kidney is extremely sensitive to the electric current. After twenty-four days, and still more completely after one month, the degenerative processes and the zones of necrosis had disappeared from kidneys treated with the scalpel, whereas in kidneys treated with the cutting current degeneration and necrosis were still present, although in less degree, throughout the duration of the observations, which was two months.

Wenzl<sup>36</sup> discussed partial resection of the kidney, which he adopted in 5 cases, with good results in 4. In the other, death occurred from septicemia.

When the kidney is irritated by inflammation and suppuration, the muscular power of the pelvis and ureter is small. It rises spontaneously if the inflammatory foci are eliminated by partial resection or by continuously repeated irrigation through a double-ended nephrostomy tube. A further rise in the muscular power of the uropoietic system can be effected by forcing fluids and by intestinal irrigations with the "enterocleaner." Irrigation acts not only by increasing the amount of fluids excreted through the kidney but by stimulating peristalsis of the excretory urinary system as well. By vigorous contractions the secreted urine is eliminated quickly without leaving residual urine; this hinders the recurrence of urinary calculi.

For prevention of recurrence of formation of stones, the following principles should be observed:

1. Renal stones should be removed before serious infections and degeneration of the kidney have occurred.
2. During operation the pelvis of the kidney should be palpated carefully, and all fragments of stone should be removed.
3. If any infection is present, permanent drainage should be established.
4. In postoperative care, antiseptic washing or treatment with bacteriophage is to be used daily.

#### URETER

*Anatomy.*—Gayet<sup>37</sup> stated that although in certain cases the intramural portion of the ureter presents the classic appearance of an ampulla

36. Wenzl, O.: Ueber die Teilresektion der Niere mit Vorschlägen zur Verhinderung des Nierensteinrezidivs, *Ztschr. f. urol. Chir. u. Gynäk.* **43**:452-475 (Nov. 15) 1937.

37. Gayet, R.: L'uretère intra-mural: Étude anatomo-physiologique. Troubles fonctionnels et leur traitement, *J. d'urol.* **44**:193-217 (Sept.) 1937.

the other hand, is much greater than elsewhere, owing to the large number of its nerve plexuses and ganglions. Its excitability is also accordingly great. Its contractility is striking, since even if isolated from the bladder and pelvic ureter it possesses autonomous movements. Tonicity reaches its maximum in this zone, as does also rhythm.

The intramural portion of the ureter plays a dual role: dynamic and tonic. The real obstacle to vesicoureteral reflux is found in the intramural portion of the ureter, and the muscle within, which opposes the reflux, is in reality the muscle of the bladder itself.

To functional disturbances of the musculature of the intramural portion of the ureter this structure reacts with anatomic modifications (hypertrophy) and physiologic modifications (hypertonia, to the point of spasm). The results of the latter are supramural retention, without narrowing of the intravesical ureter, due to simple disequilibrium of the habitual conditions of ureteral dynamism.

Functional troubles due to atony of this zone also occur. They may be congenital or acquired. They result in vesicoureteral reflux due to dilatation of the supra-adjacent urinary passages. Acquired atony may be of inflammatory or of nervous origin. Treatment is medical and surgical. Surgical treatment varies according to the case. Cystostomy will ameliorate the graver symptoms of cystitis. In cases of extreme involvement nephroureterectomy may be required, but only exceptionally.

*Anomaly.*—Lepoutre and Dewailly<sup>38</sup> made a study of extravesimal openings of the ureters of women. Such a condition is apparently of more frequent occurrence among women than among men. Disregarding exceptional cases, the ectopic ureter corresponds in about a third of cases to a simple kidney, not double; in the other two-thirds it corresponds to a double kidney one ureter of which opens normally while the other opens into the vulva or the urethra. By Weigert's law, the ectopic ureter, the meatus of which is lower, always corresponds to the uppermost of the two kidneys on the side in question. When such a ureter comes from a simple kidney it is always dilated and its parenchyma is atrophic, a point of great importance from the point of view of treatment, because its function is almost nil. Its lower orifice is narrower than a normal orifice. The ureter is dilated and sinuous as a result of defective evolution and chronic infection.

The cardinal symptom of an abnormal ureteral orifice among women is urinary incontinence, which is present from birth, is continuous and is in no way influenced by the patient's posture. In rare cases, however, this symptom does not exist.

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38. Lepoutre, C., and Dewailly, A.: Les abouchements extra-vésicaux de l'uretère chez la femme, Arch. d. mal. d. reins 10:551-562 (Nov.) 1936.



in which a positive diagnosis was made by retrograde and intravenous pyelographic studies. The condition frequently is associated with vesical hernia. It also is associated in the majority of cases with hernia of preperitoneal fat. The latter may be transilluminated, which may lead to an erroneous diagnosis of a collection of fluid in the scrotal sac.

*Ureteroenterostomy.*—Smith<sup>41</sup> stated that ureteroenterostomy in selected cases is an operation which does not carry a prohibitive risk. It was successful in 12 of the last 16 cases in which the simple unilateral technic was used. Coffey's technic no. 2 has been abandoned because of the greater mortality it entails. Ureteral drainage as proposed by Coffey should be carried out promptly if severe pyelonephritis develops. The right ureter may be implanted into the cecum if the sigmoid is not available.

*Bilharziasis.*—Vermooten<sup>42</sup> discussed bilharziasis of the ureter and reported a series of cases illustrating the stage in the progress of urinary bilharziasis at which the urologist is first consulted. This is, as a rule, eight to ten years after the original infestation; rarely are any ova present in the urine.

The diagnosis can be established only by cystoscopic examination. The cystoscopic picture associated with the various manifestations of bilharziasis is generally known. Attention, however, has not been directed toward the roentgenographic appearance of the ureter, which Vermooten<sup>42</sup> regarded as pathognomonic of the disease in its later stages.

In 1930 Harlow and Afifi drew attention to what they described as "cloudy shadows" and calcified demarcations of the bladder and the lower part of the ureter in cases of long-standing bilharziasis. In 1932 Diamantis reported a series of cases of ureteral and vesical calcification in which the condition was due to *Bilharzia haematobia*. In 1934 Afifi, describing the "roentgenographic manifestations of urinary bilharziasis," again drew attention to the "cloudy shadows" and to the "calcified demarcations" of the bladder and the ureters. Vermooten's experience with the South African type of bilharziasis indicated that the calcified demarcations in the advanced stage of the disease are rather rare, although pathologic changes in the lower part of the ureter associated with normal conditions in the proximal part, as illustrated in the urograms in his reported cases, are seen frequently.

The veins which drain the bladder also drain the pelvic portion of the ureter. From this and from general knowledge of the clinical

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41. Smith, G. G.: Recent Experiences with Uretero-Enterostomy, *Tr. Am. A. Genito-Urin. Surgeons* 30:343-346, 1937.

42. Vermooten, V.: Bilharziasis of the Ureter and Its Pathognomonic Roentgenographic Appearance, *J. Urol.* 38:430-441 (Nov.) 1937.

megaloureter the problem of management of the condition is primarily one of the efferent, rather than the secretory, integrity of the renal unit. For this reason the preservation of the secretory organ by correction of the abnormality of its conductive channels becomes a tempting problem for the urologist. This is especially so because not only is the histologic picture of the renal parenchyma practically unchanged microscopically from the normal, in cases in which no infection is present, but the total amount of renal substance which is found above such megaloureters is often about equal to that of the uninvolved kidney on the opposite side, and its secretive ability remains unimpaired for many years.

Megaloureter may be unilateral but is often bilateral. In 2 of Crabtree's cases it was associated with the lone kidney in patients with congenital absence of the other kidney. Infection was absent in only 3 of the cases which he has observed.

Five causes of megaloureter have been recognized. These are obstructions external to the bladder, ureteral stricture of the ureterovesical region, ureterocele, absence of the ureterovesical valve and neurogenic disturbances of the ureter.

The megaloureter is a changed ureter and is considered the end result of three factors: hypertrophy of the musculature of its walls, decompensation after the peak of hypertrophy has been passed and fixation caused chiefly by fibrosis and hyperplasia of the mucosa.

A survey of the literature indicates that four types of treatment have been employed for megaloureter, in addition to the obvious one of correction of pathologic changes in the urethra and the neck of the bladder. They are ureteral dilation, enlargement of the ureteral orifice by surgical operation, ureteral resection by the method of Hinman and ureteronephrectomy.

Ureteral dilation is adequate to produce great improvement in some cases of less extensively changed ureters. It cannot always be done; it is sometimes impossible either to catheterize the orifice or to produce lasting benefit even if dilation is accomplished, because dilation of some strictures produces only fracture of the walls of the stricture.

Various methods of enlarging the orifice in cases of congenital narrowing of the ureterovesical juncture have been devised. The most widely employed method is section of the orifice through the vesical wall and the nearby ureteral wall, after which the mucous membrane of the ureter is sutured to the mucous membrane of the bladder.

Hinman has contributed toward eliminating longitudinal redundancy of the megaloureter as well as toward correction of the ureterovesical defect but has not considered lateral redundancy. He has freed the ureter from the bladder, after which, either by dilatation of the orifice through the vesical wall for reinsertion of the ureter or by creation of

## PROSTATE

*Hypertrophy.*—Hinman<sup>45</sup> stated that the operation of perineal prostatectomy for hyperplasia of the prostate gland is safe. The modern method of hemostasis and plastic closure controls hemorrhage and shortens the patient's stay in the hospital by half. The functional results are as good as those achieved by any other method, if not better; and they are of equal permanence. Injury to the rectum with the formation of fecal fistula, the only actual disadvantage, is rare. The majority of such fistulas close spontaneously, and the few which do not can be closed surgically with very little risk.

The greatest advantage of the perineal operation over all others used in the treatment of hyperplasia of the prostate gland lies in the relation of hyperplasia to cancer. Cancer of the prostate gland is frequent, occurring in 14 of every 100 men more than 45 years of age. More than 1 of every 5 men who have prostatism have cancer. More than half the patients who have cancer also have hyperplasia of the prostate. Although the two lesions are distinct, any method of treatment of hyperplasia which neglects the possibility of cancer is not a good method. The perineal route is the only one by which both hyperplasia and cancer can be approached successfully at the same time. It is the only route by which a suspicion of cancer can be confirmed and by which operation best suited to all the conditions found can be carried on satisfactorily. The perineal route is the only approach by which radical removal of cancer of the prostate gland unassociated with hyperplasia can be performed with preservation of normal micturition.

Uhle and Melvin<sup>46</sup> reported a case with two recurrences of benign prostatic hypertrophy or tertiary prostatic hypertrophy.

The incidence of recurrence varies between 1 and 2 per cent. In a recent review of 227 cases of benign prostatic enlargement in which operation was done by either the suprapubic or the perineal route at the hospital of the University of Pennsylvania between the years 1923 and 1932, 3 recurrences (1.3 per cent) were observed, including that in the case reported by Uhle and Melvin.<sup>46</sup>

The surgical pathologic picture of benign prostatic enlargement precludes the removal of the prostate gland at operation. Adenomatous tissue is enucleated. Adenoma, during its period of growth, expands and compresses prostatic tissue into a thin shell resembling a capsule. To distinguish this from the true capsule of the prostate anatomists have called it the surgical or false capsule. With pressure removed, the

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45. Hinman, F.: The Modern Operation of Plastic Perineal Prostatectomy, *Tr. Am. A. Genito-Urin. Surgeons* 30:265-274, 1937.

46. Uhle, C. A. W., and Melvin, P. D.: Tertiary Prostatic Hypertrophy: An Unusual Case Report, *J. Urol.* 38:487-493 (Nov.) 1937.

The first of these was chosen. The tumor was smooth and as large as two fists. After puncture, which elicited a clear fluid, the anterior wall of the tumor was sutured to the edge of the cutaneous wound. When the cyst was opened a large amount of yellow-amber fluid escaped. The chitinous tunic was extracted in a single piece. The cyst was cleansed and drained, and a tampon was inserted. During the first month thereafter, the cavity secreted 10 to 14 cc. of fluid. Secondary hydatids were observed on several occasions and were evacuated. After eight months in the hospital the patient was discharged, at which time he had a small fistula which closed one month later. He was in good general condition and complained only of a diminution in sexual potency.

In most cases reported the clinical picture was that of compression of the urethra as well as of the rectum, the latter symptom predominating. In this case, as in others, the patient had suffered from pain in the anal region and from dysuria and pollakiuria. Except during defecation and urination, the pain had not been acute; the discomfort was more like a sense of heaviness from the pressure of a weight.

The cystoscopic picture is characteristic, showing the rounded form of the grayish red or grayish blue cyst. A transparency is seen near the free border of the tumor, and blood vessels traverse the cystic surface. In the eight operations that have been done in Russia, the transvesical route was used six times; the perineal, once, and the extraperitoneal through the abdominal wall, once. As to the mode by which the scolices penetrate the prostate gland to produce primary hydatid cyst, the possibility of their arrival through the blood stream must be excluded entirely; so the only possible way is by direct penetration of the rectal wall.

#### BLADDER

*Tumor.*—Higgins<sup>49</sup> stated that cystectomy and transplantation of the ureters had been performed in 34 of his cases of carcinoma of the bladder. A reduction in the mortality was obtained by performing the operation before dilatation of the ureters, renal infection and impairment of renal function had occurred. Less radical operative procedures should be employed in cases of advanced carcinoma of the bladder associated with dilatation of the ureters, pyelonephritis and impaired renal function. Such vesical carcinomas lie beyond the range of operability with this type of surgical procedure.

Patients who survive the operation (and the percentage of such patients is gradually increasing) have satisfactory control of the urine; they may return to their social and business activities in comfort.

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49. Higgins, C. C.: Cystectomy and Transplantation of the Ureters into the Bowel for Carcinoma of the Bladder, *Surg., Gynec. & Obst.* **66**:549-556 (Feb. 15) 1938.

palliative agent it is useful, especially in the arrest of hemorrhage, and in an occasional case sufficient regression may be accomplished thereby to render an extensive lesion more amenable to cure by other means.

Tumors which are amenable to cure by operation or by operative treatment combined with interstitial radiation are still best treated by these means. Apart from its important role as a palliative agent in cases of inoperable tumor, the greatest promise for the usefulness of high voltage roentgen therapy lies in the treatment of radiosensitive types of multiple papillomatosis of the bladder and in the treatment of those conditions, also radiosensitive, in which the tumor has involved both ureters or the region of the vesical neck.

Barringer<sup>51</sup> in a report on radium therapy in 215 cases of carcinoma of the bladder stated that his three year cures were obtained by use of radium in 69 cases, or 32 per cent. Five year cures occurred in 52 cases, or 24.1 per cent (a drop of 7.6 per cent). The total number of cases in which the bladder became free of cancer was 96, or 44.6 per cent. Treatment in these cases was by cystoscope and by suprapubic implantation. They include all cases in which the bladder was opened, no matter how extensive the disease. In many cases of extensive carcinoma, radium was implanted with the idea of controlling metastasis. Notwithstanding this, five year cures fail in about three fourths of all cases.

The factors influencing physicians' choice of therapy are the size, grade and position of the tumor and the condition of the kidneys. Small tumors, papillary or infiltrating, are best treated cystoscopically, either by implantation of radon seeds or by applications of radon. Large tumors, if papillary, are treated by suprapubic implantation of radon. Large tumors, if infiltrating, are treated by methods to be outlined. Tumors of lower grades of malignancy are treated as has been outlined. Tumors of higher grades of malignancy, particularly those of grade 4, are treated if possible by external irradiation and cystoscopically. When a tumor is on the base of the bladder (as are 75 per cent of all vesical tumors), encroaching on the ureters or internal urethra, irradiation therapy is superior to operative removal.

If the kidneys are infected and the ureters and renal pelvis dilated, cystoscopic treatment by radium is superior to the open operation. The suprapubic operation and the massive implantation of radon seeds add to the infection. The implantation or application of radium cystoscopically can be performed in divided treatments.

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51. Barringer, B. S.: Radium Therapy of Bladder Carcinoma: Five-Year Results; Failures; Future Therapy, *Tr. Am. A. Genito-Urin. Surgeons* 30:209-214, 1937.

application of a large amount of radium held against a tumor for periods of one hour by means of the cystoscope under direct vision might seem to offer a chance of controlling a large ulcerating cancer of the bladder. These treatments are supplemented by high voltage roentgen therapy. Barringer<sup>51</sup> had several cases in which this method was used and was effective.

Keyes<sup>52</sup> reported a series of 31 cases in which the patients were observed ten to eleven years after suprapubic implantation of radon seeds into epithelial tumors of the bladder too extensive for control by cystoscope.

Prompt control of recurrences prevents increase in malignancy. Ten cases of grade 1 and grade 2 tumors were reported. In half these cases the tumor recurred, and in 2 cases the patients died of the disease. Yet, thanks to routine cystoscopic studies, half of these patients have been free of tumor for a number of years, and in 2 others the condition has been controlled by cystoscopic observation during the ten years in which the tumors have continued to recur. Tumors of grades 3 and 4 show much less tendency to recur; if not palpably infiltrating they may be controlled in the majority of cases. Of 6 patients, 4 were free of tumor when last seen or heard from, a number of years after operation.

Infiltration palpable on preoperative rectal or abdominal examination is a sign that the tumor is incurable. In this series only 1 such tumor was controlled. Three of the patients died of cancer of the prostate gland. Although necropsy was not performed, the cancer in 1 case was believed to be secondary to a tumor of the bladder or of the urethra.

Deming<sup>53</sup> described a new surgical approach for treatment of carcinoma of the neck of the bladder. A patient who had cancer of the vesical neck and was treated with radical perineal excision of the vesical neck, part of the trigon, the prostate gland and seminal vesicles was reported well after a period of six years. Restoration of normal urination was secured. The comfort of the patient after this operation was extraordinary as compared with the discomfort of the long period during which the patient usually suffers from dysuria after treatment with radium. The technic of the operation is not difficult. Total cystectomy with transplantation of the ureters is not necessary for certain types of cancer which develop at the vesical neck. Radical perineal resection of the vesical neck and the prostate gland for cancer of the vesical neck should be employed more often than has been customary.

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52. Keyes, E. L.: Thirty-One Patients with Bladder Tumor Treated Ten Years Ago by Suprapubic Section and Radon Implantation, *Tr. Am. A. Genito-Urin. Surgeons* 30:215-221, 1937.

53. Deming, C. L.: Successful Radical Perineal Resection of Bladder Neck for Carcinoma, *Tr. Am. A. Genito-Urin. Surgeons* 30:227-234, 1937.

no further symptoms from the diverticulum. The prostate gland, which was enlarged, was removed two months afterward by transurethral resection. Searching the literature; Hryntschak found that in a few cases the condition had been treated in the same manner and with good results; always, as in his case, the operation had been done as a makeshift procedure.

The excellent result obtained in his case by exclusion and drainage of the diverticulum combined with transurethral resection of the vesical neck convinced him that this is the best method of procedure in similar cases.

*Injury.*—Stevens and Delzell<sup>57</sup> stated that rupture of the bladder is to be distinguished from perforation. The mortality from the former is higher than that from the latter. Twenty-seven cases of all types of vesical injury involving rupture or perforation are reported. Eight of 14 patients who had intraperitoneal injury died, but death occurred in only 2 of 13 patients who had extraperitoneal injury alone.

Roentgenographic methods are theoretically preferable in arriving at a diagnosis, but cystoscopic study has been applied more readily, and it has given a positive diagnosis in nearly 85 per cent of cases. If operation is performed promptly, we doubt whether it adds to the risk. Diagnosis by catheter is notoriously unreliable. The treatment is to operate promptly and to establish efficient drainage of the site of injury and of the bladder. Stevens and Delzell<sup>57</sup> preferred suture of the traumatic opening, but this is not always essential. Exploratory laparotomy is important, especially in the early stages. Transfusion or treatment of shock may be required before operation can be considered.

*Exclusion.*—Henry Wade<sup>58</sup> reviewed his 60 cases of exclusion of the bladder by diversion of the urinary stream, into the colon in 54 cases, to the surface of the skin in 5 and into a fistula in 1. He concluded that the Coffey-Mayo technic or Coffey's technic no. 1 is the best and that technics no. 2 (tube technic) and no. 3 (transfixion suture) are unsound in principle and inferior in many ways to no. 1. Since 1934 he has performed bilateral simultaneous implantation made possible by immediate intravenous infusion of sodium sulfate solution as advocated by I. L. Dick. This promotes renal secretion and prevents anuria. In the 54 cases of transplantation to the bowel, 36 transplantations have been bilateral and simultaneous, without the use of catheters. Ten additional transplantations have been done for patients who had single kidneys.

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57. Stevens, A. R., and Delzell, W. R.: Traumatic Injuries of the Bladder, with Report of Twenty-Seven Patients Operated Upon, *Tr. Am. A. Genito-Urin. Surgeons* **30**:185-196, 1937.

58. Wade, H.: Vesical Exclusion, *Proc. Roy. Soc. Med.* **31**:277-292 (Jan.) 1938.

caused by ascending urinary infection. Gironcoli, in discussing his experience, stated:

The construction of an intestinal bladder is a serious operation, serious in itself and the more so because it is done usually on cachectic patients. To reduce risk, the operation is done in stages. By this method of multiple operation, much time is lost and the patients suffering from carcinoma of the bladder become more and more cachectic, as they derive no benefit from the preparatory operations. Even when a well functioning intestinal bladder is constructed, the patient may die from infection of the urinary tract.

#### URETHRA

*Tumor.*—Mortensen<sup>61</sup> reported a case of carcinoma of the male urethra. The rarity of the condition, coupled with the inaccessibility of the usual site of its occurrence, that is, the bulbous urethra, renders early diagnosis extremely difficult. In addition, the lesion almost invariably is grafted on some more chronic and more frequent lesion in this situation.

Histologically, carcinoma of the urethra must be distinguished carefully from carcinoma arising in the penis, the prostate gland or Cowper's gland and also from secondary involvement of the urethra from these regions. A large percentage of urethral carcinomas are of the squamous cell type, the occurrence of which in a site normally lined by transitional epithelium is explained by the process of epithelial metaplasia. The frequent occurrence of pathologic changes in epithelium leading to the development of leukoplakia, discovered in routine urethroscopic examination for the diagnosis and treatment of chronic urethral infections, stresses the importance of this factor. The papillary type of tumor is found less frequently; it is often observed in younger patients, with whom it is of more rapid growth and of greater malignancy. True adenocarcinoma of the urethra has been described on only 2 occasions. It arises from the glandular structures of the urethra.

In most cases the results of treatment are poor, and in by far the greater number of cases reported the patient has died shortly after diagnosis has been made, whether or not surgical intervention was employed.

Harbach<sup>62</sup> stated that primary carcinoma of the male urethra is of a low degree of malignancy, is slow to metastasize and, owing to its situation, is particularly suitable for resection. It is apparently a disease of middle age, although Paton reported its occurrence in a youth aged 18 and Kroiss in a man aged 91. The chief difficulty is in diagnosis, and

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61. Mortensen, H.: Carcinoma of the Male Urethra, with Report of a Case, *Brit. J. Surg.* **24**:669-675 (April) 1937.

62. Harbach, F. O.: Primary Carcinoma of the Male Urethra, *J. Urol.* **38**: 311-315 (Sept.) 1937.



information. It is as well fitted for diagnostic and roentgenologic purposes as for therapeutic injections. Of the utmost importance is the systematic study of the seminal vesicles, filled with a contrast medium, before fluoroscopic examination is performed. Such observations indicate whether clinical healing is taking place or whether surgical intervention is necessary.

#### PENIS

*Erythroplasia.*—Dean and Farrow<sup>65</sup> stated that erythroplasia of the penis is a form of erythematous dermatosis which affects the glans and the mucous surface of the prepuce. It is likely that the condition is the result of chronic irritation beneath a tight prepuce. Although the subjective symptoms are usually mild and the lesions appear insignificant, carcinomatous degeneration has been noted in about 40 per cent of reported cases. The microscopic picture is that of chronic inflammatory precancerous dermatosis. The clinical course is characterized by slow but steady extension and by a complete lack of favorable response to treatment with any topical application. In the case reported intense surface irradiation after circumcision was followed by healing. No evidence of relapse was present after more than a year.

*Plastic Restoration.*—Brown<sup>66</sup> reported 4 cases of restoration of the entire skin of the penis. In 3 of the 4 instances, free thick split skin grafts gave permanent healing with complete normal sensation and function. In the fourth case, split grafts were used to supplement scrotal flaps and to repair the defect of the scrotum.

In preparing for the graft the superficial granulation tissue and deep scar tissue are carefully dissected away in layers until the penis can be elongated completely, extreme care being used not to enter either the corpora cavernosa or the urethra. The next most important step is to obtain a free thick split skin graft, of about one-half to three-fourths the thickness of the skin of the thigh, in one piece, large enough to cover the penis completely without the necessity of patching. A catheter is inserted, and an assistant holds the penis completely extended on the catheter. The graft is wrapped carefully and smoothly around the penis, the edges being overlapped to assure complete coverage. It is then sewed accurately in place all around the penis, at the corona and at the abdomen, and then down the line of the overlapping edges, with fine horsehair on fine needles. Fine mesh gauze is wrapped smoothly around the extended penis; a gauze flap is then wrapped securely on with a sterile bandage, so that the penis is held in complete extension on the catheter.

65. Dean, A. L., Jr., and Farrow, J. H.: Erythroplasia of the Penis, Tr. Am. A. Genito-Urin. Surgeons **30**:405-416, 1937.

66. Brown, J. B.: Restoration of the Entire Skin of the Penis, Surg., Gynec. & Obst. **65**:362-365 (Sept.) 1937.

From 2 to 11 per cent of malignant renal tumors occurring in children are hypernephromas. This type of tumor appears to be more frequent among girls. Hematuria is the dominant early symptom of hypernephroma in children, in contrast to the initial symptom of a mass in the loin, such as occurs with Wilms' tumor. Hematuria or a mass in the region of the kidney will direct attention to the urinary tract, but the diagnosis will rest chiefly on retrograde pyelographic studies.

Embryonal adenomyosarcoma (Wilms' tumor) is the most frequent neoplasm (one fifth of all tumors) of the urinary tract and abdomen occurring in young persons. Seventy-five per cent of Wilms tumors appear before the fifth year of life, and two thirds of them appear before the third year, which is the average age at which the tumors are first recognized. These growths have been observed in the fetus. After the seventh year, hypernephroma is more likely to occur than embryonal adenomyosarcoma.

A fifth of the patients who have Wilms' tumor have metastasis. The spread is characteristically through the blood stream, yet by lymphatic or direct extension the liver, the spleen, the spine, the intestine, the diaphragm and the lungs may be invaded. A tumor in the region of the kidney is the usual early sign of Wilms' tumor. Pain occurs in about 35 per cent of cases of Wilms' tumor. It results principally from capsular tension consequent to the enlarging parenchymal growth. Pain due to mass, weight or abdominal pressure is also frequent. Hematuria occurs late and is present in only about 15 per cent of cases. This is in contrast to its high incidence in cases of renal hypernephroma.

If there is doubt as to the correct diagnosis, a biopsy may be performed on material obtained by aspiration. The center of the tumor mass is determined by triangulation from a study of the urogram, and into this central region a needle (18 gage) attached to a 5 or 10 cc. syringe is plunged. Moderate suction is applied as the needle is introduced, and when it is at the desired depth the suction is increased sufficiently to draw out tissue for microscopic examination.

When only the usual surgical treatment, nephrectomy, is employed, the mortality is about 95 per cent. Only 5 of 55 patients lived longer than one year, a mortality of 91 per cent. The average life expectancy after nephrectomy alone is eight months; recurrences of the tumor are usually found after four months.

Preoperative radiation therapy apparently is a desirable addition in the treatment of this condition. In the employment of irradiation in treatment of the young, due caution must be observed, and vital organs, such as the liver, the spleen and the opposite kidney, must be protected. If the child withstands the treatment well, the total dose may be increased or the therapeutic period prolonged. After preoperative radiation the optimal time for operation appears to be from three to six

growth, in which cases development of the genital tract and sexual precocity are striking manifestations. The important malignant adrenal tumor among children is neuroblastoma or neurocytoma, and, according to Campbell's observation, it occurs fully a third as often as do malignant renal tumors. Removal of the growth is the proper treatment, but in the case of adrenal tumor, too, intensive irradiation preoperatively and postoperatively, with divided doses, appears to offer the only hope for the reduction of the extremely high mortality.

#### UROLOGIC SURGERY

Priestley<sup>70</sup> stated that in 1936, 841 operations exclusive of transurethral procedures were performed on 758 patients for disease of the genitourinary system. There were 15 deaths in the entire group, or a gross mortality of 1.9 per cent.

Of the 245 patients who underwent operations on the kidney, 5 died, giving a mortality of approximately 2 per cent. Of patients who had operations on the kidney, 116 were operated on for nephrolithiasis. The next most frequent condition which required operation was hydronephrosis. Various changes have been instituted in the general management of nephrolithiasis in the past year. From the surgical point of view, a more thorough effort than ever before is being made to determine whether any obstruction to free renal drainage is present at the same time that stones are removed from the kidney. If obstruction is found, it is corrected when the stones are removed; therefore, plastic procedures now are combined with pelviolithotomy more frequently than in the past. Treatment of the infection which so frequently is associated with nephrolithiasis has undergone decided changes in the last year. It now includes the use of sulfanilamide and its derivatives and the continued use of mandelic acid and nonspecific injections of neoarsphenamine. These methods of treatment have supplanted largely the more cumbersome and difficult ketogenic diet.

Among the 47 patients operated on because of hydronephrosis, nephrectomy was performed on 31 and plastic procedures on the remaining 16. Of 29 patients on whom nephrectomy was performed for malignant tumors of the kidney, preoperative radiation was employed only in treating Wilms' tumor among children. Our experience with preoperative irradiation for adenocarcinoma or hypernephroma of the kidney among adults has not been as satisfactory as that reported by certain authors elsewhere. Among the 64 patients who underwent operation on the ureter there were 3 deaths. Ureterolithotomy was performed in 43 instances without a death. Two deaths occurred following transplantation of the ureter to the sigmoid flexure of the colon.

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70. Priestley, J. T.: Review of Urologic Surgery for 1936, Proc. Staff Meet., Mayo Clin. 12:675-677 (Oct. 27) 1937.

In 749 cases, 835 resections of the prostate gland were done for benign or malignant enlargement causing obstruction to the flow of urine. It is interesting to note that only 3 per cent of the patients were less than 50 years of age, whereas 14.6 per cent were over 75. The average age for the entire group was 66.

The period of postoperative hospitalization was one week or less in 38.4 per cent of cases and more than three weeks in only 3.1 per cent.

The amount of tissue removed during the course of operation is interesting. In 211 cases it was 25 Gm. or more; in 1 instance 100 Gm. was removed at a single operation.

The mortality rate for the patients who underwent prostatic resection was a little higher than in preceding years. A total of 11 deaths occurred in the series of 749 cases, a mortality of nearly 1.5 per cent. There was no mortality with any of the other procedures.

#### CHYLURIA

Takahasi and Ikeda <sup>72</sup> were able to cure chyluria in a fair percentage of their cases (in all of which the condition was probably caused by filariasis) by simple injections of Ringer's solution into the renal pelvis. In 2 cases catheterization of the ureters alone was sufficient to produce this effect. Patients who were not cured were at least benefited by this treatment, as chyluria ceased for from five days to a year. The authors stated that hyperemia and stasis due to the injected solution or to catheterization tend to destroy the existing fistula between the lymphatic vessels and the renal pelvis. The condition is cured only when it is of recent occurrence; older processes are resistant to this form of treatment.

Wakefield and Thompson <sup>73</sup> reported a series of 5 cases of non-parasitic chyluria. Although more than 100 cases of nonparasitic chyluria have been reported in the literature, a critical review probably would exclude many of them, for only with extreme difficulty can the absence of *Filaria bancrofti* be proved. The diagnosis of nonparasitic chyluria can be made only after one is definitely sure that there has been no chance of exposure to filarial infestation. The voiding of chylous urine is the only symptom of the disorder. Coagulation of the urine before it is voided usually produces discomfort. The malnutrition of the patient can hardly be attributed to the loss of fat in the urine, for the equivalent of 400 calories is an unusually large output.

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72. Takahasi, S., and Ikeda, K.: Heilung der Chylurie durch Nierenbeckeneinspritzung von physiologischer Kochsalzlösung, *Ztschr. f. Urol.* **31**:729-736 (Nov.) 1937.

73. Wakefield, E. G., and Thompson, G. J.: Nonparasitic Chyluria, *J. Urol.* **38**:102-110 (July) 1937.

sulfanilamide has been administered by mouth. They found that sulfanilamide is more effective in urine which has an alkaline reaction than in that which is acid. It was observed, too, that sulfanilamide in higher concentrations acts bactericidally in acid urine. The present study was undertaken for the purpose of determining the effectiveness of lower concentrations of sulfanilamide as a urinary antiseptic. Experiments were conducted by adding known quantities of sulfanilamide to samples of urine which contained certain types of bacteria. A comparison of the bactericidal action of free sulfanilamide added to the urine with that of the free and conjugated forms as excreted in the urine after administration of the drug by mouth also was made. It was found that the conjugated form seemed definitely more bactericidal than the free sulfanilamide. The following conclusions were reached:

1. In its free form, concentrations of only 25 to 40 mg. of sulfanilamide per hundred cubic centimeters of urine when added to an alkaline urine act bactericidally; concentrations as low as 25 to 30 mg. when excreted in alkaline urine act bactericidally.

2. The acetylated form of sulfanilamide does not act bactericidally in urine at a  $p_H$  of 7.8 at a concentration up to 200 mg. per hundred cubic centimeters.

#### UROGRAPHY

Stevens<sup>76</sup> stated that excretory urographic study furnishes sufficient data for exact diagnosis in a limited number of cases; in the others it must be supplemented by retrograde injection.

Better visualization of the renal cortex after excretory urographic examination is an important factor in the diagnosis of tumors of the kidney that do not involve or exert pressure on the renal pelvis or calices.

It is impossible to perforate a normal renal pelvis with an ordinary ureteral catheter. Extreme gentleness should be employed in the catheterization and injection of fluid into the renal pelvis when the patient is an infant or a young child. Injury to the kidney and also back flow are frequent during retrograde pyelographic examination.

Filling the kidney pelvis to the point of discomfort is sometimes a dangerous procedure. The principal danger accompanying extravasation into the parenchyma of the kidney and in the various types of back flow is the possible dissemination of infectious material.

Rupture extending through the capsule of the kidney is the most dangerous complication associated with retrograde pyelographic study.

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76. Stevens, W. E.: *Roentgenologic Examination of the Kidney with Special Reference to Backflow and Injuries Associated with Retrograde Pyelography*. Tr. Am. A. Genito-Urin. Surgeons **30**:169-182, 1937.

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Fig. 1.—Section through the rectus muscle of a hypoproteinemic dog;  $\times 920$ .

means of correcting, temporarily at least, the hypoproteinemic state. The lyophile process of preserving plasma described by Florsdorf and Mudd<sup>7</sup> provides plasma in such a state that it can be shipped to isolated communities and kept for months at refrigerator temperature for immediate use. In addition to these advantages, it can be given intravenously

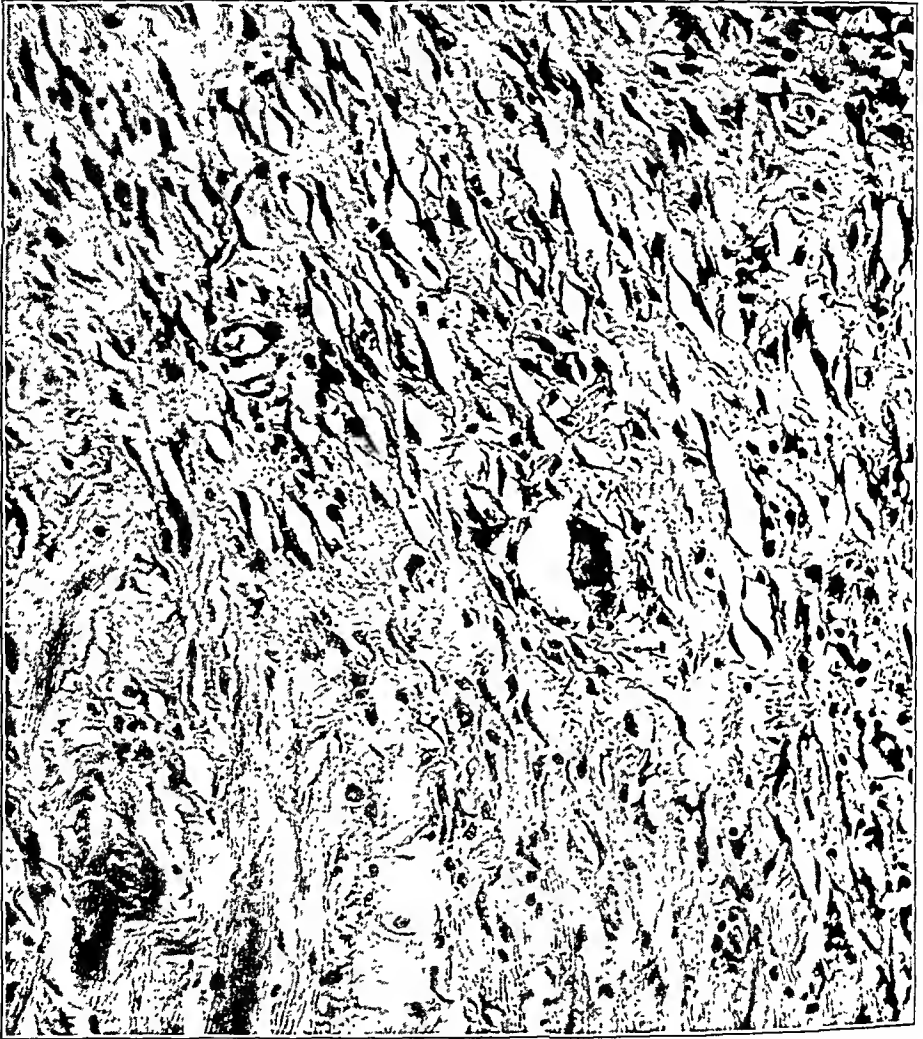


Fig. 4.—Section ( $\times 200$ ) through a fourteen day old wound, showing well developed fibroplasia with excellent wound healing.

as a hypertonic solution. This has two merits: Not only does it rapidly replenish the protein deficit, but, being given as a hypertonic solution, it

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7. Florsdorf, E. W., and Mudd, Stuart: Procedure and Apparatus for Preservation in "Lyophile" Form of Serum and Other Biological Substances, *J. Immunol.* 29:389, 1935.

rapidly increases the osmotic pressure of the blood, thus efficiently overcoming any tissue edema which may be present.

The interesting observation was made during this work that although the serum proteins were within normal limits, some intercellular edema

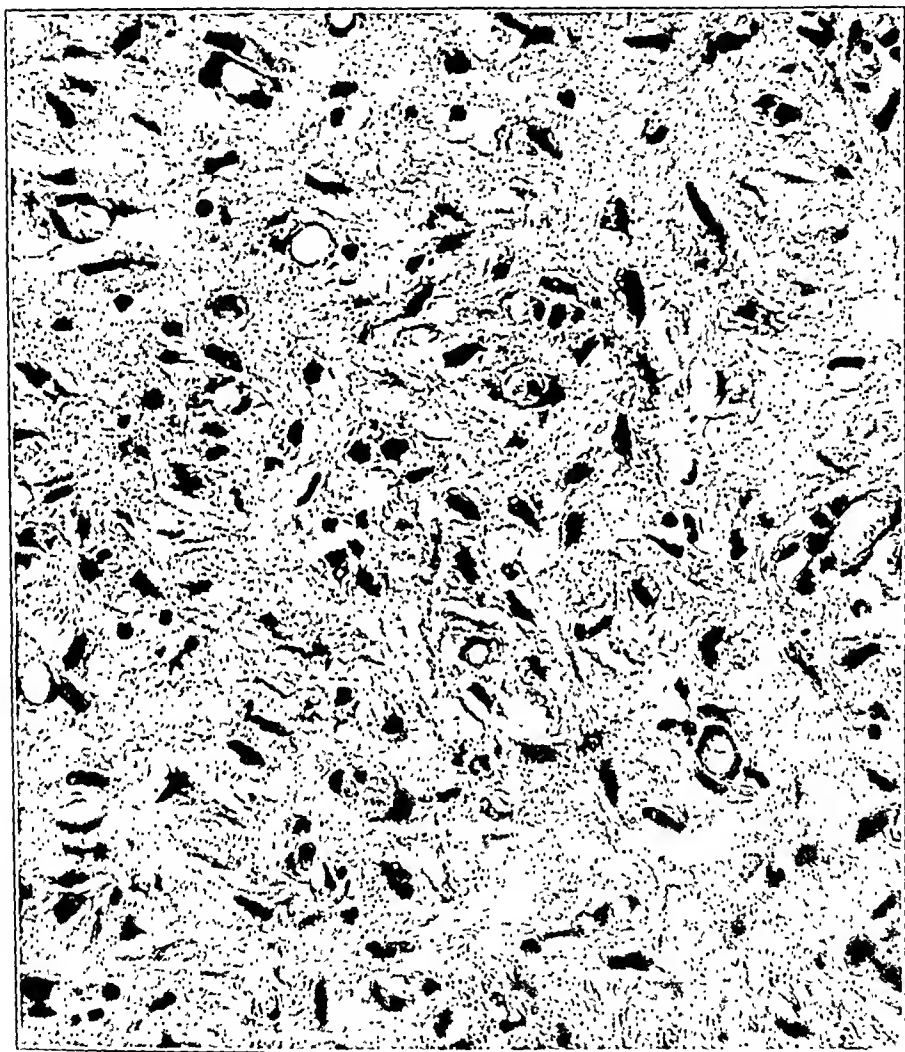


Fig. 5.—Section ( $\times 400$ ) through a fourteen day old wound, showing well developed fibroplasia. The new capillaries are clearly visible.

along the line of incision was still evident seven days after operation. This edema was probably associated with the trauma of operation. Nevertheless, fibroblastic repair was in progress in spite of the edema, indicating that, at least in these dogs, the edema per se did not inhibit repair of the wound.

From the results of our experiments with catgut, which showed that decrease in the tensile strength of the catgut increases with the degree of hypoproteinemia, it seems advisable to use a nonabsorbable suture material in cases of protein deficiency. If this is inadvisable because of fear of infection, the layer sutures of catgut should be reenforced by stay sutures of nonabsorbable material.

#### SUMMARY

1. Retardation in healing of wounds associated with hypoproteinemia in dogs may be averted by restoration of the serum protein to normal levels immediately after operation.
2. The decline in tensile strength of catgut in dogs was accelerated by induction of hypoproteinemia, although this may have been due in part to the greater tendency to infection at the junction of the skin and catgut.
3. The advantages of lyophilized serum or plasma for restoring the concentration of the blood proteins are pointed out, and the practicability of the method is demonstrated for dogs.

## ILIOPECTINEAL BURSITIS

JEROME G. FINDER, M.D.

CHICAGO

The syndrome of iliopectineal bursitis may be overlooked easily in making a differential diagnosis of lesions of the hip joint if its likelihood is not kept in mind. This point is well illustrated by the occurrence of a large tumor mass in the right groin of an elderly man. Competent internists, surgeons and orthopedists examined the mass and made several diagnoses, but iliopectineal bursitis was not mentioned, even indirectly. As a matter of fact, the correct diagnosis was established by operation and by a study of the literature, which confirmed my opinion that this disease has not received the clinical attention that it deserves.

### REPORT OF A CASE

T. L. was first seen in the orthopedic outpatient clinic in December 1926 at the age of 49. The history and symptoms were fairly typical of slowly progressive hypertrophic arthritis involving many joints over a period of years; the right hip joint was especially troublesome. During the examination a swelling the size of a lemon was noted in the right inguinal region. According to the patient, it had been present for twenty years (since 1906), developing two years after he had been kicked by a horse. There had been a short period of pain following the trauma, but the swelling itself had been painless thereafter. However, he was aware of some radiation of pain in the anterior part of the hip joint when the arthritis was more severe.

For nine years nothing further was heard from the patient. When he returned in November 1935 he stated that he had been in poor health for about one year. He could walk with great difficulty in a stooped position but preferred to stay in bed or in a wheel chair. He had been losing considerable weight and had a persistent irritating cough. He said that the mass in the right groin had reached the size of a grapefruit in 1934 and had grown somewhat larger since then.

On physical examination he presented an advanced Bechterew type of spondylitis deformans. Both hips were contracted 35 degrees in flexion. In the right groin a firm semisolid tumor, the size of a large grapefruit, elevated and displaced the femoral sheath and its contents medially. The overlying skin was streaked by a number of thin blue veins but was not adherent to the tumor beneath (fig. 1).

Roentgenograms confirmed the diagnosis of arthritis of the spine and hips. The tumor in the groin cast a slight soft tissue shadow only. Roentgenograms of the chest showed pulmonary areas which might be interpreted as circumscribed lesions. The laboratory findings were as follows: blood pressure, 136 systolic and

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Read before the Chicago Orthopedic Society, Chicago, Dec. 11, 1936. The material for this paper was obtained from the files of the Department of Orthopedic Surgery, Children's Hospital, Iowa City, service of Dr. Arthur Steindler.

90 diastolic; hemoglobin content, 53 per cent; red blood cells, 2,600,000; white blood cells, 7,800, with a normal differential count; Kahn and Wassermann reactions negative, and urine, normal.

On the basis of the large tumor mass, which had recently enlarged, the loss of weight, the secondary anemia, the cachectic appearance of the patient, the persistent cough and the suggestive pulmonary lesions, the diagnosis considered most likely was fascial sarcoma of the right inguinal region with metastases to the lung. This diagnosis was practically discarded a few days later when the tumor was aspirated and 210 cc. of clear, viscid yellow fluid was drawn off. The tumor refilled within ten days. Culture of the fluid was sterile. A guinea-pig inoculated with the fluid was killed after six weeks; no pathologic changes were found at autopsy.

In view of these findings, an exploratory operation was performed on Feb. 7, 1936, just thirty years after the tumor was first noted. A 1 per cent solution of procaine hydrochloride was employed as a local anesthesia, and an incision was made parallel and lateral to the femoral sheath. The skin, subcutaneous tissues and thinned out layers of the sartorius and iliopsoas muscles were retracted. A firm white fibrous capsule formed the external wall of the tumor. On incision, 500 cc.

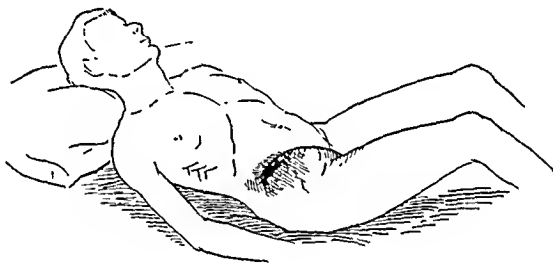


Fig. 1.—Sketch of the patient showing the enlarged right iliopectineal bursa, which fills in the pelvofemoral region; the hips are in flexion contracture.

of fluid, similar to that previously aspirated, gushed out. An elliptic portion of the roof of the wall of the tumor was resected for histologic study.

When the depths of the cavity were sponged dry, a smooth-walled, shining internal lining was exposed. In the lateral portion of the floor of the sac was a tiny valvelike flap overlying a 3 to 4 mm. opening which communicated with the hip joint. When the hip was passively moved, synovial fluid was seen to pass from the joint through the opening into the sac cavity.

The communicating tunnel and the adjacent portion of the bursal floor were resected, and the capsule was sutured tightly across the defect so as to obliterate the passage between the joint and the bursa. No attempt was made to resect the bursa, but its walls were everted and the medial fibers of the sartorius and iliopsoas muscles were anchored into the floor of the sac, furnishing a surface for adhesions and absorption. In a similar manner, the medial superficial fascial layers were anchored into the floor. The wound was then closed tightly by approximation of the superficial tissues and skin.

The histologic examination of the roof of the bursa showed a wall composed of dense fibrous tissue. The innermost lining layers were not differentiated into a definite synovial membrane but were arranged compactly in strata parallel to the surface and represented pressure layers (fig. 2). The next layers outward were

formed of looser elastic tissue with occasional infiltrating round cells. The most external layers of the wall were more or less vascular, merging into the subcutaneous tissues.

An interesting finding was the inclusion of numerous small calcified fragments in the lining layers of the bursa, with foreign body giant cells in relation to them. These calcified bodies probably represented tiny pieces of calcified cartilage or bone sand which were the product of grinding down of an osteo-arthritic joint. During motion, they were subsequently washed into the bursal sac, where they became incorporated into the fibrous tissue of the lining layers.

Sections from the floor of the sac at the site of opening into the joint were similar to those just described. In addition, however, there was a well formed,

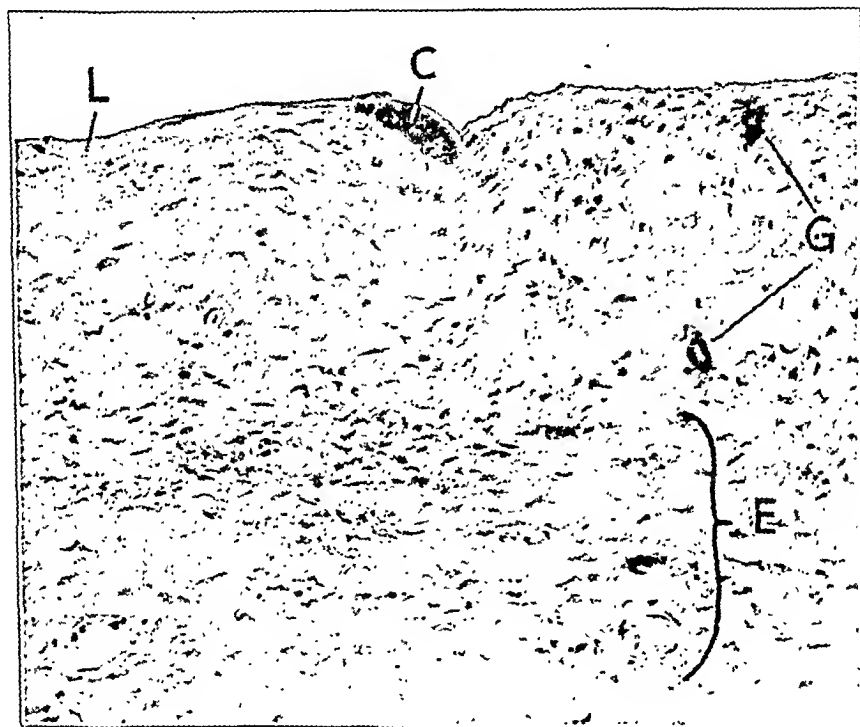


Fig. 2.—Photomicrograph of the bursa. The superficial lining of the bursa (*L*) is composed of compact fibrous tissue in parallel pressure layers, within which a small calcified body (*C*) has just been incorporated; giant cells (*G*) are seen in relation. The more external layers (*E*) are looser in structure and contain small blood vessels.

somewhat hyperplastic synovial membrane which represented the lining on the joint surface of the specimen.

*Progress Notes.*—The wound healed by primary intention, and the sutures were removed on the seventh day. Subsequently the patient was transferred to the medical department, where he became progressively worse due to chronic nephritis and died in uremic coma on April 22. The amyloidosis of the kidney, liver and spleen, diaphragmatic hernia, ulcerative esophagitis and pulmonary congestion and edema found at autopsy explained the confusing clinical symptoms. Exploration



of the iliopectineal bursa (two and one half months after operation) showed effective obliteration of the cavity by scar tissue. There was no sign of reestablishment of the communication with the hip joint.

#### ANATOMY

All anatomists<sup>1</sup> describe the iliopectineal bursa, although some do not designate it specifically; iliopsoas bursa and bursa mucosa subiliaca are synonyms. The iliopectineal bursa is a constant structure and is said to be the largest bursa normally present. Kessel<sup>2</sup> definitely demonstrated its presence in the 25.75 mm. embryo. The iliopsoas muscle covers the anterior aspect of the capsular ligament of the psoas muscle and the joint capsule. The bursa is bounded anteriorly by the iliopsoas muscle; posteriorly, by the pectineal eminence and thin portion of the capsule of the hip joint; laterally, by the iliofemoral ligament; medially, by the cotyloid ligament; above by Poupart's ligament, and below, by the pubofemoral ligament.

The anterior crural nerve lies deeply between the fleshy and the tendinous portion of the iliopsoas muscle. The femoral artery, enclosed within the crural sheath, rests on the psoas magna muscle. The femoral vein, similarly enclosed, lies between the psoas magnus and the pectineus muscle (fig. 3).

In some cases the cavity of the iliopectineal bursa is directly continuous with that of the joint. The portion of the capsule between the iliofemoral (Y) and the pubofemoral (pubocapsular) ligament is very thin, and at this point the bursa is in intimate relation with the synovial membrane of the hip joint. Either the fibrous capsule or the synovial membrane or both may be defective, permitting communication between the two cavities. Kessel found such communication in 15 per cent of 535 adult anatomic specimens. Most of these are probably congenital, but trauma or friction may also tend to establish the communication.

The bursa, when pathologically enlarged, may extend far beyond its normal confines. Durville<sup>3</sup> stated that its upper limit does not extend above the inguinal ligament; Lund,<sup>4</sup> on the contrary, said that it might

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1. Buchanan, A. M.: *Manual of Anatomy*, Chicago, W. T. Keener & Co., 1906, vol. 1, p. 438. Cunningham, D. J.: *Manual of Practical Anatomy*, ed. 8, revised and edited by Arthur Robinson, Baltimore, William Wood & Company, 1927, vol. 1, p. 278. Gray, Henry: *Anatomy of the Human Body*, ed. 21, revised by Warren H. Lewis, Philadelphia, Lea & Febiger, 1924, p. 468. Heisler, John C.: *Practical Anatomy*, ed. 2, Philadelphia, J. B. Lippincott Company, 1920, p. 224. Spalteholz, Werner: *Hand Atlas of Human Anatomy*, ed. 4, Philadelphia, J. B. Lippincott Company, 1923, vol. 2, p. 350.

2. Kessel, F.: Ueber die Bursa mucosa iliopectinea, ihre Entwicklung und ihre Kommunikation mit der Kapsel des Hüftgelenkes, *Morphol. Jahrb.* 58:413, 1927.

3. Durville, cited by Gatch and Green.<sup>9</sup>

4. Lund, F. B.: Iliopsoas Bursa, *Boston M. & S. J.* 147:345, 1902.

extend up into the iliac fossa. It may enlarge sideways from the iliopectineal eminence to the anterior superior iliac spine. The lower border may reach into the region of the trochanter minor of the femur. On dissection, the ordinary bursa is usually large enough to admit the index finger easily for exploration of its cavity. When distended, the bursa assumes surprising dimensions (fig. 4). The bursae which are reported in the literature are usually as large as a hen's egg or a goose egg.

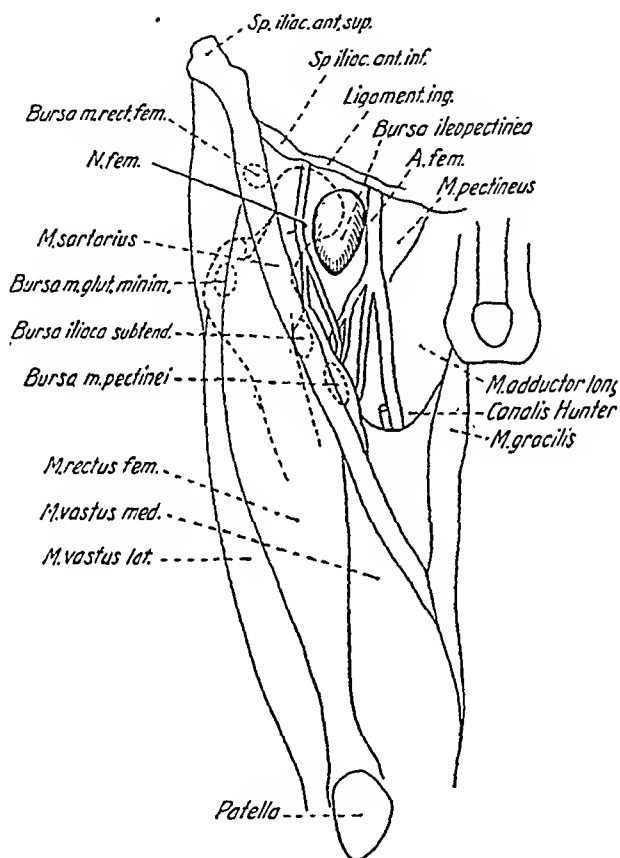


Fig. 3.—Diagram showing the relationship of the iliopectineal bursa to the other para-articular bursae, femoral nerve and vessels and femur. (From Timmermann, H. W.: Ueber die Bursitis ilio-pectinea, Med. Klin. 29:1172 [Aug. 25] 1933.)

However, Cullen<sup>5</sup> reported a tumor in a male which occupied nearly one half of the pelvis and contained six large calcified cartilaginous masses. Charleston<sup>6</sup> described a bursa which extended from the pelvis, above Poupart's ligament, to the region of the knee joint.

5. Cullen, T. S.: A Large Cystic Tumor Developing from the Ilio-Psoas Bursa, J. A. M. A. 54:1181 (April 9) 1910.

6. Charleston, cited by Gatch and Green.<sup>9</sup>

## REVIEW OF THE LITERATURE

The first description of the iliopectineal bursa appears in Vesalius' "De humani corporis fabrica" written in 1555, according to Kessel.<sup>2</sup> However, the first clinical case of iliopectineal bursitis was reported by Frücke<sup>7</sup> in 1834. During the next one hundred years thirty-five additional cases were added. Zuelzer<sup>8</sup> in 1899 wrote a classic on the subject of iliopsoas and trochanteric bursitis, reviewing fourteen cases gathered from the literature. In 1925 Gatch and Green<sup>9</sup> completed a survey of twenty-four cases, including one of their own. Finally, O'Connor,<sup>10</sup> in an excellent treatise, demonstrated the practical application of his

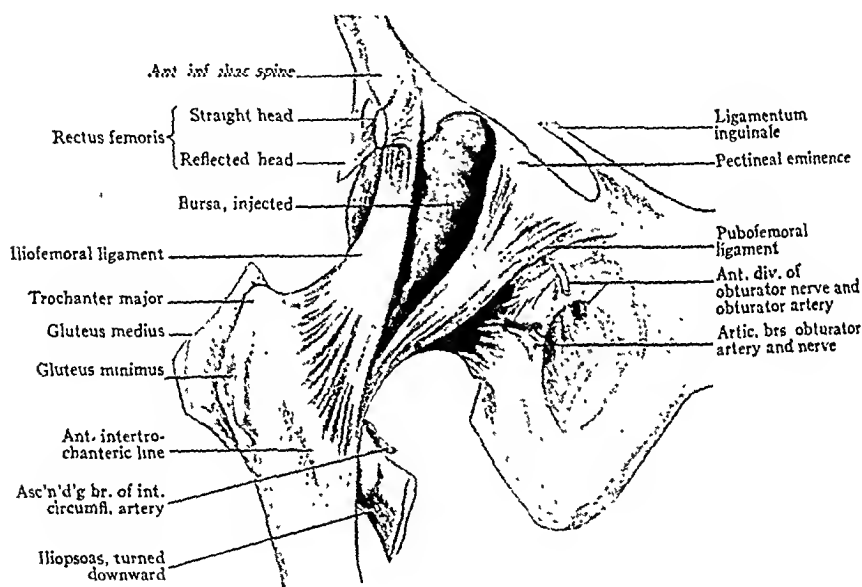


Fig. 4.—The injected iliopectineal bursa in relation to the ligamentous structures around the hip joint. (From Heisler, John C.: Practical Anatomy, ed. 2, Philadelphia, J. B. Lippincott Company, 1920, p. 224.)

experience by reporting thirty-three personal observations. The seven cases proved at operation lends credence to the accuracy of O'Connor's diagnoses in the remaining twenty-six instances.

7. Frücke, cited by O'Connor.<sup>10</sup>

8. Zuelzer, R.: Die Schleimbeutel der Hüfte und deren Erkrankungen, Deutsche Ztschr. f. Chir. 50:148, 1899.

9. Gatch, W. D., and Green, W. T.: Cysts of the Ilio-Psoas Bursa, Ann. Surg. 82:277, 1925.

10. O'Connor, D. S.: Early Recognition of Iliopectineal Bursitis, Surg., Gynec. & Obst. 57:674, 1933.

## ETIOLOGY

Earlier authors classified these bursae as simple cysts or inflammatory bursae of specific or nonspecific origin. Blood-borne infection, septice-mia, gonorrhea, typhoid, syphilis and tuberculosis were considered as causative agents. However, these causes are the exception rather than the rule. I consider two factors important: arthritis and trauma, frequently in combination. Gatch and Green stated that without exception investigation in cases of a rheumatic condition disclosed a communication between the hip joint and the bursa. Therefore, it seems logical to assume that the inflammatory condition of the synovia of the joint would be mirrored in the bursal lining.

Trauma is the most important single factor in the development of iliopectineal bursitis. The male sex is therefore more often heir to this lesion than the female sex. Only three of the thirty-six cases reported up to 1935 were in women, excluding O'Connor's series in which eleven of the patients were women and twenty-two were men. Bursitis may be caused among middle-aged men performing heavy labor by multiple minute occupational injuries, the result of constant friction from the overlying psoas tendon. On the other hand, the history of trauma may be definite. A severe blow may affect the bursa directly; usually the injury is indirect, due to violent muscular activity. The mechanism consists of a sudden forceful hyperextension at the hip by a backward thrust of the body weight, frequently in the process of lifting some heavy object. As O'Connor pointed out, when the hip is flexed the iliopsoas muscle and the attached anterior portion of the bursa ride away from the joint. When the hip is suddenly hyperextended, the tension stresses which stretch the psoas muscle also stretch or traumatize the bursa.

## PATHOLOGIC PICTURE

The first stage in the production of any bursitis is an inflammatory reaction to an exciting agent, whether it is toxic, chemical, mechanical or bacterial. Effusion results, and the bursa becomes distended. Rarely, hyperplastic synovitis or serositis with villi formation may develop in a bursa, but usually the bursal lining is adventitious; a true endothelial or mesothelial serous membrane has not been proved definitely. The tendency is rather for degenerative changes to take place in the superficial lining layers with the formation of a fibrin or fibrinoid substance that ultimately undergoes colliquation. The problem is still unsettled and is outside the province of this paper.

The presence of calcified foreign bodies in the bursa is interesting and represents an osteochondromatosis of the synovial bursa. This localization in the periarticular and juxta-articular bursae is much rarer

than in the articular synovia. Ardouin<sup>11</sup> in 1934 could find reports of only five cases in the inguinal region. Two sources of bursal bodies are possible: the bursal wall and the structures of the hip joint. The bursal wall may give rise to large bodies by a metaplastic process. Smaller bodies may result from degenerative changes in the bursal wall due to pressure. The affinity of necrotic tissue for lime salts is well known, and on this basis calcium may be precipitated in the bursal wall. In such cases the roentgenograms may possibly show an increased density in the outlines of the bursa.

When the calcified bodies originate from the structures of the hip joint, there is usually an antecedent trauma or osteo-arthritis, frequently both. Marginal lippings or exostotic spurs may chip off under stress of motion of the joint and be carried through a communicating aperture into the bursal sac, where they may enlarge by further deposition of calcium. As a rule, however, these foreign bodies are taken up by the fibrous tissue of the superficial layers of the bursal lining. This process is illustrated in my case report.

#### SYMPTOMS

The onset of symptoms in cases of iliopectineal bursitis due to trauma usually is acute and is characterized by rather severe pain in the groin. It is aggravated by movements of the hip, particularly extension, and is relieved by rest with the hip flexed. The involved area may show a fulness that is warm to the touch and tender to pressure. The gait is hampered by a limp. Applications of heat and rest, without weight bearing, usually alleviate the symptoms within two weeks. However, discomfort may persist if chronic bursitis develops.

In many instances iliopectineal bursitis is more insidious in its progress; it may follow some half-forgotten accident or unnoticed repeated minor occupational injury. Pain, which develops gradually, is first noticed after the fatigue of a day's labor. Later, efforts of rising from bed or from a chair evoke pain in the inguinal region. In addition to the direct pain caused by the bursitis, the patient may also complain of pain referred to the front of the knee as it radiates along the irritated femoral nerve. Timmermann<sup>12</sup> wrote that occasionally pain also radiates to the abdomen or the back. A limp impedes the gait because of the tendency to relax the psoas muscle by flexion of the hip. Ultimately, dragging of the extremity, limp, stumbling and weakness indicate atrophy and loss of muscle power of the psoas muscle, as O'Connor<sup>10</sup> observed.

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11. Ardouin, G.: *L'osteochondromatose des synoviales et des bourses séreuses*, Rev. d'orthop. **21**:301, 1934.

12. Timmermann, H. W.: *Ueber die Bursitis iliopectinea*, Med. Klin. **29**:1172 (Aug. 25) 1933.

On examination, point tenderness may be elicited on pressure just below Poupart's ligament half way between the symphysis pubis and the anterior superior iliac spine (fig. 5). This site lies medial to the femoral nerve and lateral to the femoral artery. Pain is usually felt on active motion and less frequently on passive motion of the hip joint. The position of relief is assumed in flexion, external rotation and abduction.

In a significant number of cases a tumor is palpable, often visible, at the site of chronic bursitis. As a rule the tumors are quite tense, often suggesting the presence of a solid tissue neoplasm. However,

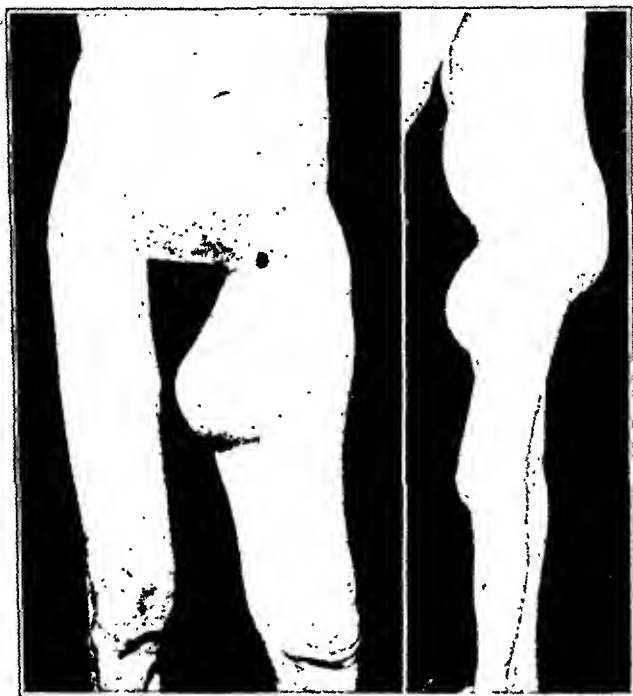


Fig. 5.—Patient with Pott's disease in the lumbar region with a large psoas abscess on the left side. For orientation, a black spot marks the site of tenderness due to iliopectineal bursitis. Compare the side view of the psoas abscess with that of the iliopectineal bursa depicted in figure 1.

O'Connor states that of ten of the cases in his series in which tumefaction was present, the swelling was fluctuant in six.

#### DIAGNOSIS

The diagnosis of iliopectineal bursitis may be made on the history of a direct blow in the groin or of a sudden hyperextension force at the hip. Pain develops below Poupart's ligament at a point half way between the anterior superior iliac spine and the symphysis; this spot is tender to pressure. Relief is sought by the patient's assuming the

position of flexion, external rotation and abduction. In cases in which the condition is of longer standing, a tumor is palpable. A clear fluid may be aspirated, but in the rare case of suppurative or tuberculous bursitis cloudy material with inflammatory cells and positive bacterial cultures may be found.

When a swelling is present, other lesions must be differentiated. Hernia may be ruled out by its reducibility, the transmission of the cough wave and its infrequent impediment of the motion of the joint. Tuberculosis of the spine or sacro-iliac joint explains the usual psoas abscess (fig. 5); the pea-soup pus and its bacteriologic composition confirm the diagnosis. Sworn<sup>13</sup> reported three cases of acute psoas abscess, from which *Streptococcus haemolyticus*, *Staphylococcus aureus* and *Bacillus influenzae*, respectively, were isolated. Roentgenograms of the spine and pelvis were normal. However, the acute abscess, unlike the chronic tuberculous type, tracks outward into the sheath of the iliacus muscle and seldom passes deep to Poupart's ligament into the thigh. Malignant conditions develop insidiously, the patient declines rapidly, metastases may appear and biopsy is confirmatory. Dilatation of the femoral vein, aneurysm of the femoral artery and certain types of inguinal lymphadenopathy are less common.

In the absence of swelling, osteo-arthritis should be considered. Frequently, it is concomitant with bursitis and cannot be excluded. However, the greater age of the patient, the frequent involvement of several joints, the more lateral localization of pain over the neck of the femur (Duvernay<sup>14</sup>), the position of deformity in flexion, external rotation and adduction and the roentgenographic picture furnish points of differentiation. Primary psoitis occurs in childhood and in adolescence (Ingelrans and Minne<sup>15</sup> and Klages<sup>16</sup>) but is seen occasionally in later life. Trauma is followed by a limp and radiating pain in the leg. Lordosis in the lumbar region increases, the inguinal lymph nodes enlarge and fever develops. A flexion, abduction and external rotation contracture develops, as in iliopsoas bursitis, but the hip joint is free. The roentgenogram may show a definitely enlarged psoas shadow. Transitory synovitis of the hip joint is essentially a disease of childhood

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13. Sworn, B. R.: Acute Psoas Abscess, *Brit. M. J.* 2:6 (July 1) 1933.

14. Duvernay, cited by Burckhardt, Hans: Arthritis deformans und chronische Gelenkkrankheiten, in von Bruns, P.: *Neue deutsche Chirurgie*, Stuttgart, Ferdinand Enke, 1932, vol. 52, p. 362.

15. Ingelrans, P., and Minne, J.: Onze cas de psoïtis primitives observés chez des enfants et des adolescents, *Rev. d'orthop.* 20:577, 1933.

16. Klages, F.: Nichttuberkulose Psoaserkrankungen im Kindesalter, *Beitr. z. klin. Chir.* 158:171, 1933.

(Finder<sup>17</sup>). Appendicitis or ureteral calculus must be ruled out, according to Timmermann,<sup>12</sup> especially when the pain of iliopectineal bursitis is referred to the abdomen or back.

#### TREATMENT

In the early stages of bursitis the most important factor is rest in bed. Relief may be afforded by permitting flexion, but relaxation of spastic structures by simple traction with Buck's extension is preferable. Heat may hasten resolution, although occasionally cold compresses give more comfort. Aspiration relieves tension temporarily. Cure should not be expected from repeated aspirations of the larger bursae; this procedure failed in all of those cases in which it was performed.

Gatch and Green<sup>9</sup> stated that all authors are agreed on the excision of the chronically enlarged iliopectineal bursa. Unquestionably, total extirpation will cure the lesion, but it may require tedious, cautious dissection because of the important structures adjacent. The method of obliterating the sac worked out satisfactorily in my case. It recommends itself by virtue of its simplicity. One detail is important: any possible communication between the hip joint and the bursa must be eradicated.

#### COMMENT

Iliopectineal bursitis is a rather frequent lesion, but unfamiliarity with the early symptoms has undoubtedly caused the condition to be classified erroneously many times. This disease bears close resemblance to a number of conditions about the hip joint, and the differential diagnosis requires a nicety of distinction. When the bursa becomes enlarged, the lesion should be recognized without difficulty.

From the economic standpoint, it is important to diagnose the lesion in its early stages. Since bursitis often has an occupational traumatic origin, it becomes incumbent on the physician to recognize and treat the condition adequately early; to minimize its seriousness or to neglect its treatment often means the development of chronic bursitis with prolonged disability, convalescence and, not infrequently, the need for surgical intervention.

#### SUMMARY

The iliopectineal bursa is a constant anatomic structure, which often communicates with the hip joint.

Bursitis is frequently the result of trauma.

Iliopectineal bursitis occurs with relative frequency but goes unrecognized because its symptoms resemble those found with a number of more common lesions about the hip joint.

17. Finder, J. G.: Transitory Synovitis of the Hip Joint in Childhood, *J. A. M. A.* 107:3 (July 4) 1936.



Treatment in the early stages is conservative. With the development of an enlarged, chronically irritated bursa, surgical treatment may be necessary. The method of obliteration is successful; it is suggested in preference to the more difficult procedure of total removal of the bursa.

An unusual case of iliopectineal bursitis is reported here.

55 East Washington Street.

## A REVIEW OF UROLOGIC SURGERY

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*(Concluded from page 372)*

### BLADDER

*Tumor.*—Wolfe<sup>44</sup> stated that routine cystoscopic examination has revealed tumor of the bladder as an occupational disease in workers exposed to benzidine, alphanaphthylamine and betanaphthylamine but not in those exposed to aniline. Analysis of the records of 2,868 routine cystoscopic examinations and of 83 cases of tumor of the bladder indicates that history and symptomatology are of little aid in diagnosis. Constant exposure to the cancerigenic agent is the important factor in the development of tumor of the bladder. Routine cystoscopic examination is the most important procedure in the medical control of the so-called aniline tumor of the bladder.

Ferguson,<sup>45</sup> in discussing aniline tumor of the bladder, stated that he believed that the pathogenesis of multiple papillomatosis of the bladder, both occupational and nonoccupational, is the result of the circulation, a cancerigenic agent in the blood. Because of this, he expressed the belief that the entire bladder should be treated with divided doses of

44. Wolfe, H. D.: Routine Cystoscopic Examination as a Control Measure in Anilin Tumor of the Bladder, *J. Urol.* **38**:216-220 (Aug.) 1937.

45. Ferguson, R. S.: Clinical Significance of the Anilin Tumor of the Bladder, *J. Urol.* **38**:243-250 (Aug.) 1937.

roentgen rays in order that the later appearance of new tumors in other locations may be prevented in a high percentage of cases. Application of this thesis to date has resulted in an increase in the percentage of complete regression of the primary tumors and a definite decrease in the appearance of recurrent new tumors in such cases.

Washburn <sup>46</sup> discussed the treatment of aniline tumor of the urinary bladder. In a group of 86 cases there were 9 deaths, a mortality of approximately 10 per cent. Twenty-four (28 per cent) of the patients had been treated too recently for a consideration of the end-results, and 53 men (62 per cent) were free from tumor. This is a creditable showing when one considers that there were 15 patients with extensive highly malignant lesions. It is to the credit of the dye industry that full responsibility has been accepted, that every facility has been provided for the discovery of early cases and that nothing has been left undone to restore the affected men to health.

Gay <sup>47</sup> stated that the disease produced by exposure to aniline affects the entire bladder and most frequently occurs in the lower half of the viscus above the level of the ureteral openings. The sequence of events is as follows: First, there is endothelial proliferation in focal subepithelial blood vessels. Occlusion of a vessel causes dilatation of afferent capillaries and edema of the surrounding tissue. Ectasia and proliferation of the capillaries form a mass of vessels; this mass may persist for months, or proliferation of the basal layer of the overlying epithelium may occur, with the formation of a tumor. The initial epithelial tumor may be of any degree of malignancy but tends to become more malignant with the passage of time. The sequence of vascular and epithelial lesions may be repeated indefinitely, and various stages of development as well as different grades of tumor may coexist.

Evans <sup>48</sup> stated, after making a study of cases of aniline tumor of the bladder, that an analysis of the literature fails to show conclusively either the carcinogenic agents or the mechanism of action in the production of such tumors. Analysis of a series of 83 cases of tumor of the bladder indicates that the tumors occur in persons who have been exposed to benzidine, betanaphthylamine, alphanaphthylamine and other nitro and amino compounds, while those exposed only to aniline have shown no tumors. The majority of the tumors appear after from six to twenty years of exposure. The average time is twelve years. The incidence of tumor is higher in persons from 40 to 60 years of age; an appreciable

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46. Washburn, V. D.: The Treatment of Anilin Tumors of the Urinary Bladder, *J. Urol.* **38**:232-242 (Aug.) 1937.

47. Gay, D. M.: Pathology of Anilin Tumor of the Bladder, *J. Urol.* **38**:221-231 (Aug.) 1937.

48. Evans, E. E.: Causative Agents and Protective Measures in the Anilin Tumor of the Bladder, *J. Urol.* **38**:212-215 (Aug.) 1937.

number occur in those from 30 to 40 years of age. Repeated cystoscopic examinations are essential in the medical control of employees exposed to aniline, benzidine, betanaphthylamine and alphanaphthylamine. Adequate methods of control are dependent on proper methods of production, careful medical supervision and a better understanding of the mechanism of production of the tumors through research.

Leadbetter and Colston<sup>49</sup> reported a case of metastasis to the brain from carcinoma of the bladder and discussed 6 similar cases, Reports of which were collected from the literature. Their survey of the literature indicates the rarity of cerebral metastasis from tumor of the bladder.

In an analysis of 625 reported cases of tumor of the bladder in which necropsy was performed, Leadbetter and Colston found metastasis to the brain in only 2, an incidence of only 0.3 per cent, while the incidence of metastasis in general was greater than 30 per cent. The records of the Brady Urological Institute showed that in over 800 cases of tumor of the bladder metastasis to the brain was encountered clinically only twice.

Weyerbacher and Balch<sup>50</sup> reported a case of leiomyosarcoma of the bladder and reviewed the literature. Reports of only 4 cases were found. The total of 5 cases comprise approximately 2 per cent of all types of sarcoma of the bladder.

Leiomyosarcoma has been found in many organs of the body other than the urinary tract. Krauskopf collected from the literature reports of 31 cases in which various organs were involved. The uterus was the seat of the lesion in 15 instances. The urinary tract appears to possess more immunity against the onslaughts of leiomyosarcoma than does the reproductive tract of the female. Besides the bladder, the only other structure of the urinary tract in which leiomyosarcoma is reported is the kidney. Leiomyosarcoma may occur during infancy or old age and may attack either the male or the female.

During the early stages these tumors manifest themselves in no way peculiar to epithelial neoplasms. Frequency, urgency and hematuria in some form or another have been present in every case. Frequency is the most prominent symptom, probably due to an associated cystitis. Straining and dribbling may occur due to mechanical obstruction of the neck of the bladder. Cystography and cystoscopy will demonstrate the tumor, if they can be successfully carried out, but it is questionable whether a mesothelial or an epithelial tumor can be correctly differentiated. If a glistening, shiny and smooth neoplasm is seen, a mesothelial neoplasm

49. Leadbetter, W. F., and Colston, J. A. C.: Brain Metastasis in Carcinoma of the Bladder, *J. Urol.* 38:267-277 (Sept.) 1937.

50. Weyerbacher, A. F., and Balch, J. F.: Leiomyosarcoma of the Bladder, with Report of a Case and a Review of the Literature, *J. Urol.* 38:278-287 (Sept.) 1937.

should be suspected. The surgical attack on a mesothelial tumor of the bladder differs in no way from that on an epithelial growth. Removal or destruction of the tumor in the most suitable manner adapted to the given case is the method of choice.

White and Gaines,<sup>51</sup> in an article on spindle cell sarcoma of the bladder, question whether all reported cases are true to type. They reported a case of sarcoma of the bladder in a man aged 38; after removal of the tumor, recurrence took place rapidly. Several sections of the growth were examined microscopically, and a diagnosis was made of transitional cell sarcoma with sarcoma-like areas. It was stated in the literature that of 69 patients with tumor of the bladder who were operated on, only 3 were considered cured; they were followed for a period of from three to twelve years. Liberal resection of the tumor-bearing wall of the bladder or complete cystectomy and urethral transplantation may result in cure in a case in which diagnosis is made early. However, only about 8 such cases have been recorded in the medical literature.

After a résumé and consideration of some practical points in the pathologic structure, symptoms and diagnosis of tumor of the bladder, Millin<sup>52</sup> discussed in some detail the treatment, emphasizing especially his method of endoscopic endothermic resection. The procedures available for the treatment of tumor of the bladder are:

1. High voltage roentgen treatment or distant radium treatment
2. Treatment by the urethral approach
  - (a) Diathermic coagulation with either the bipolar or the monopolar current
  - (b) Endothermic resection
  - (c) Introduction of radon seeds
  - (d) Aspiration of a bulky friable tumor (Born)
  - (e) Chemotherapy, consisting of the direct application of trichloroacetic acid (Joseph)
  - (f) A combination of two or more of the foregoing methods
3. Treatment by the suprapubic approach
  - (a) Partial cystectomy or segmental resection
  - (b) Total cystectomy with implantation of the ureters in the bowel or the skin
  - (c) Diathermic coagulation
  - (d) Endothermic resection
  - (e) Implantation of radium
  - (f) Application of actual cautery
  - (g) Low voltage roentgen therapy direct to the tumor with the Choaul applicator
  - (h) Permanent cystostomy
  - (i) A combination of two or more of the foregoing methods

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51. White, E. W., and Gaines, R. B.: Spindle Cell Bladder Sarcoma, *Surg., Gynec. & Obst.* **65**:366-369 (Sept.) 1937.

52. Millin, Terence: Tumours of the Urinary Bladder with Description of a New Endoscopic Technique, *Brit. J. Surg.* **25**:145-171 (July) 1937.

When pain is a marked feature and uncontrolled by the appropriate use of one of these methods of treatment, a neurosurgical attack by one of the following methods may be indicated: (1) presacral neurectomy, (2) the intradural injection of alcohol or (3) lateral chordotomy.

Selection of treatment will depend on: (1) the nature of the tumor, as evidenced by the cystoscopic picture or by microscopy of sections; (2) the size of the tumor; (3) the situation of the tumor, and (4) the associated complications, either within or without the urogenital tract. In the end, personal prejudices will weigh heavily with each individual surgeon in his selection. Millin stated that the results of high voltage roentgen therapy alone are disappointing, although its use postoperatively is advised. Transurethral coagulation is the best method for accessible tumors of relatively low malignancy. However, because of the necessity of repeated sésances in the treatment of large tumors and the likelihood of transplantation with repeated instrumentation, transurethral endothermic resection is an ideal method for the treatment of a large number of tumors, both benign and malignant.

Because of the limitations of the Stern-McCarthy resectoscope in removing tumors other than those situated around the orifice of the bladder, Millin has devised an operating cystoscope of convex sheath pattern with a foroblique telescope and a retrograde visual system. A number of various sized loops are used as electrodes, depending on the size of the tumor under revision. Resection is carried out as in the corresponding operation for prostatic obstruction. When the tumor is removed, the base is coagulated. Endothermic resection is contraindicated for: a tumor so situated that a relatively safe segmental resection may be done; a tumor within or about a diverticulum; an extensive growth which needs suprapubic section, as does a growth associated with prostatic obstruction when the gland is large; a tumor that is vascular and bleeds readily on urethral instrumentation, and a tumor on the anterior surface about the orifice of the bladder.

Most British urologists have largely dispensed with the use of radium in treating tumors of the bladder. Their present position in regard to the use of radium, either the element or its emanation, may be summed up by saying that it is not required in treating papillary growths; the results, both immediate and remote, are superior with partial cystectomy, electrocoagulation or endothermic resection. Inoperable infiltrating carcinomas are not cured with radium.

Cade's technic, consisting in a skilfully applied barrage of needles, with screening of from 0.8 to 1 mm. of platinum, left in situ for ten days, does cause marked regression of some radiosensitive tumors. Burns following inadequate screening may cause an intolerable cystalgia and urinary frequency.

On the basis of the results of treatment in 172 cases of vesical tumor, Millin concluded that the prognosis in cases of solitary papilloma is relatively good. With transurethral diathermic treatment, 65 per cent of the patients were free from recurrence at the end of three years. He considered the prognosis in cases of multiple papillomas to be grave. Only 4 patients were free from recurrences three years after diathermic destruction of multiple tumors.

The results following open operation for papillomas are disappointing. The outlook with endoscopic endothermic resection is much better.

Pfahler<sup>53</sup> stated that only about a fourth of the patients who have carcinoma of the bladder can be treated surgically without interference with the urethra or ureters; therefore, three fourths of the patients should be treated by irradiation. Treatment with highly filtered high voltage roentgen rays seems to accomplish more satisfactory results than other methods, especially in the inoperable group of tumors. This treatment involves less suffering and less interference with the daily habits of the patient than any other form of treatment. An insufficient number of patients have been treated by this method to make statistics of any value, but Pfahler estimated that one may expect disappearance of the tumor in from 30 to 50 per cent of cases.

After irradiation there is generally a cessation of hematuria at the end of three or four weeks. This does not indicate, however, that the disease has disappeared.

Cystitis is likely to be a complication before, during and after the roentgen therapy and must be dealt with just as cystitis would be treated under any other conditions. Anemia must be counteracted.

Pfahler aims to give the planned treatment within a month, which means from 20 to 25 treatments, but this number may have to be doubled or tripled. It is desirable to give as little treatment as will accomplish the results. The more accurately the disease is localized and the less its extent, the smaller will be the portals through which irradiation is given and the more one can conserve the normal tissues. On the other hand, if one confines treatment to too small an area, some remnant of the disease will be missed and recurrence will follow.

Mark<sup>54</sup> reported a case of endometriosis of the bladder in a patient whose chief complaints were hematuria, frequency, dysuria and disabling pain, these symptoms occurring with cyclic regularity and starting five months after hysterectomy. Because of the presence of endometriosis in the resected portion of the bladder, extending down to the perito-

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53. Pfahler, G. E.: The Diagnosis and Treatment of Tumors of the Bladder by Means of Roentgen-Rays, *Surg., Gynec. & Obst.* **64**:989-994 (June) 1937.

54. Mark, E. G.: Endometriosis of the Bladder, *J. Urol.* **37**:799-807 (June) 1937.

neum, although this was not involved, and the absence of adhesions from the cervical stump or other pelvic structures to the bladder, this condition could be classified as "primary endometriosis" of the bladder. Mark expressed the belief, however, that viable endometrial tissue was implanted in the serosa of the bladder at the time of hysterectomy.

The great preponderance of reports of endometriosis of the bladder have come from the German clinics, where most careful observations have been carried out, both clinically and in the taking of the history. This led Mark to believe that such a finding should not be so rare as has been reported in the English and the American literature.

Shaw<sup>55</sup> described an operative technique for partial cystectomy, with reimplantation of the ureter into the bladder by the perineal approach, that has been performed successfully on the living subject. This procedure appears adaptable to infiltrating carcinomas limited to the base and to the orifice of the bladder that are not resectable by the suprapubic approach.

A man aged 63 was found on cystoscopic examination to have a necrotic papillary carcinoma involving the left ureteral orifice and the greater portion of the trigon and extending through the dilated internal sphincter into the prostatic urethra, almost to the level of the verumontanum.

The operation was performed with the patient under spinal anesthesia and in the perineal position. The usual inverted V incision was made, as is done in Young's radical operation for carcinoma of the prostate. The operation was carried out in the same manner as is the radical operation for carcinoma of the prostate, with the exception that the urethra was cut off in its prostatic portion instead of in its membranous portion. The pelvic fascia was separated laterally and anteriorly until the tractor could be felt through the anterior wall of the bladder. A transverse incision was then made through the wall of the bladder at its junction with the prostate, and the tractor was pulled down so as to give a complete exposure of the entire interior of the bladder. The distal edges of the cut bladder were grasped with Allis forceps and pulled downward, exposing the vas deferens on the right and the ureter and the vas deferens on the left. The left ureter was cut across flush with the external surface of the wall of the bladder, and a catgut ligature was placed through its tip. The arteries of the seminal vesicles were then ligated and divided, and the vasa deferentia were cut. The excised tissue contained all the prostate except the apex, the greater portion of the trigon, the left ureteral orifice and both seminal vesicles. Closure of

55. Shaw, E. C.: Perineal and Vaginal Cystectomy with Transplantation of the Ureters, *J. Urol.* 37:850-857 (June) 1937.



the bladder was begun with a row of sutures on the left side at the point of the greatest defect, the lateral walls being brought down medially to form a new floor. This line of interrupted chromic catgut sutures was continued until the opening of the bladder had been reduced to such size that it could be attached to the cut off apex of the prostate by a circular row of sutures. Two drains were placed in the wound, and the levator ani muscles were approximated with two sutures of chromic catgut. A no. 22 French catheter was left in the bladder.

Cystoscopy was performed at intervals of three months for the first two years after the operation and annually until five years had elapsed. There was no recurrence of the tumor and no history of further urinary difficulties.

Bumpus<sup>56</sup> reported a series of cases of tumor of the bladder from the Los Angeles County General Hospital. Destruction with diathermy was used in 77, in 34 through the urethra and in 43 by transvesical exposure. Eleven of the patients in the former group were living from three to five years after transurethral electrocoagulation—apparent cures in 33 per cent. These figures indicate how uncertain ultimate recovery is once a diagnosis of tumor of the bladder has been made. Unquestionably, the poor final results were due in no small measure to the failure of the patients to come for reexamination.

Of the latter group of 43 patients treated transvesically, 25 had tumors of the papillary type; 16 of these patients are known to be dead and 5 were alive over three years. Of the 18 patients with infiltrating tumors, 10 are known to be dead and but 1 was alive over three years. Fourteen patients, or 35 per cent, died as a result of the operative procedure. Since there were 6 patients alive from three to five years and 24 were known to be dead, there would seem to be approximately a 25 per cent possibility of relief by this method of treatment, which is apparently as high an incidence of possible cure as is to be expected by any method of treatment now known. In the series of cases in which transvesical exposure was used the ureteral orifice was included 29 times in the cautery destruction, and in 10 cases the involvement of the orifice was considered a decided factor in the unsatisfactory convalescence if not a direct cause of the patient's death.

Ward<sup>57</sup> reported 7 cases of tumor of the bladder in which cystectomy with transplantation of the ureter was successful. Previously reported statistics have been quite unfavorable. Zukerkandle collected reports

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56. Bumpus, H. C., Jr.: What We May Expect from Treatment of Bladder Tumors, *California & West. Med.* **47**:84-87 (Aug.) 1937.

57. Ward, Bernard: Total Cystectomy with Transplantation of the Ureters into the Pelvic Colon for Malignant Growth of the Urinary Bladder, Based on an Experience of Seven Successful Cases, *Proc. Roy. Soc. Med.* **30**:137-156 (Dec.) 1936.

of 64 cases from the literature, with a mortality of 50 per cent, and in 42 cases cited by Scheele the mortality for the one stage operation was 53.5 per cent. Walters operated in 76 cases of exstrophy of the bladder, in which there were 3 deaths, or a mortality of 3.9 per cent.

Ward reported 11 cases in which cystectomy was performed, with 3 deaths, or a mortality of 7 per cent. A modification of the Coffey technic of ureteral transplantation was done on 5 of Ward's patients. One lived five years, 1 a year and a half and 1 a year and nine months, and 1 died of other conditions a short time after operation. The other 2 patients had been operated on only a short time before the report was published.

*Exstrophy.*—Ladd and Lanman<sup>58</sup> presented their observations on 15 patients with exstrophy of the bladder on whom 30 ureterosigmoidostomies were performed. Methods used for treatment of exstrophy of the bladder at the Children's Hospital, in Boston, before 1930 were unsatisfactory. The operative mortality was high due to peritonitis. Postoperative renal function was often impaired to a considerable degree by infection of the urinary tract. Methods then advocated to avoid peritonitis and infection of the urinary tract and to insure urinary flow were time consuming, complicated and ill suited to the age group at the hospital. According to the authors, the chief difficulties and dangers in operative treatment of exstrophy of the bladder by uterosigmoidostomy are peritonitis that results from leakage or soiling at the site of anastomosis, obstruction of the urinary outflow at the site of anastomosis and infection of the urinary tract, with its resulting renal damage.

Experimental work on animals by Lanman and Colby from 1928 to 1930 demonstrated that if each ureter was transplanted separately any possible slight temporary impairment of urinary outflow through the side anastomosed was safely compensated for by the opposite side. Immediate postoperative peritonitis was more common when some mechanical guide through the site of the anastomosis was used, and postmortem examinations seemed to indicate that this foreign body was often a causative factor. Moreover, postmortem examinations at a later date on animals that survived showed, both grossly and histologically, that there was more infection of the urinary tract when a guide was used than when it was not. It seemed clear that if the two stage operation was performed, there was no need to fear obstruction to the urinary outflow if a guide was used. It also seemed clear that the use of a guide was not only unnecessary but dangerous. It was concluded, therefore, that the two stage operation, without the use of catheters or guides, offered the best method to minimize and prevent the dangers of peritonitis, urinary obstruction and infection of the urinary tract.

58. Ladd, W. E., and Lanman, T. H.: *Exstrophy of the Bladder*, New England J. Med. 216:637-644 (April 15) 1937.

In their summary the authors stated that they considered the following principles fundamental in obviating these dangers: a two stage operation for the ureteral transplantation; transplantation of the right ureter first and of the left, from two to four weeks later; a transperitoneal approach for ureterosigmoidostomy, no catheter or guides being left but the proximal end of the ureter being opened widely by a longitudinal slit; no drainage of the peritoneal cavity; removal of the bladder as soon as is practicable after the ureteral transplantation and the selection of patients preferably between 3 and 5 years of age.

With the technic of Ladd and Lanman, the actual transplantation of the ureter is done transperitoneally, as the dangers of peritonitis are considered far less than the dangers resulting from a rather blind extraperitoneal approach. In using the extraperitoneal approach it is impossible to be sure that the ureter lies in a straight line from the kidney and that it is free from all tension and kinking. The transperitoneal approach is especially important in transplanting the left ureter, which is done from two to four weeks after transplantation of the right ureter. Intravenous pyelograms in the cases in which this technic was used showed excellent results two years after operation, especially when compared with the results following the earlier types of this operation. There were no fatalities, and good control of the bowel was obtained in every case. Ladd and Lanman advised, however, not doing the operation until the child is from 3 to 5 years of age, as by that time the patient can cooperate in acquiring control over the rectum.

Intravenous pyelograms and determinations of the blood chemistry were made with reported cases. These were normal in enough cases to lead the authors to state that preoperative infection of the urinary tract is a rarity. Later infection of the urinary tract is more likely to occur with the so-called aseptic type of extraperitoneal operation than with an operation that strives to have the course of the ureter into the bowel as straight and as unobstructed as possible.

*Ulcer.*—Folsom and O'Brien<sup>59</sup> gave a preliminary report of their observations on 7 cases of Hunner ulcer in which absolute alcohol was injected into and about the ulcers. Gas anesthesia was used for all the patients. Injections were made with a long flexible needle through the McCarthy panendoscope. From 2 to 6 cc. was injected, 0.2 cc. being introduced at each puncture. These injections were distributed about and directly into the ulcer. After the treatment the patients spent from sixteen to twenty-four hours in bed and were then able to resume their regular activities.

According to Folsom and O'Brien, definite conclusions are not warranted on the basis of their brief report in which observations were

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59. Folsom, A. I., and O'Brien, H. A.: Transvesical Alcoholic Injection for Elusive Ulcer of the Bladder, *J. Urol.* **37**:808-814 (June) 1937.

made over such a short period of time. They were impressed, however, by the prompt relief their patients received and stated that such immediate relief can be expected in a large majority of cases. They expressed uncertainty as to the duration of the period of relief, but expressed the opinion that with added experience their injections should be more complete, thereby increasing the length of this period. Finally, they have been reassured by the lack of evidence of damage to the wall of the bladder from the alcohol. With care to prevent rupture of the bladder from overdistention, it would seem that the procedure is entirely free from danger.

*Fistula.*—Walters<sup>60</sup> presented 2 cases of recurring vesicovaginal fistulas in which successful transperitoneal repair was done. By means of his technic, each fistula is closed individually, and an omental flap is sutured between the bladder and the vagina. It would appear that such a method might be applied in the treatment of certain vesicovaginal fistulas which have heretofore been thought to be inoperable and for which ureteral transplantation to the sigmoid flexure was carried out.

*Bladder Dysfunction.*—Thomson-Walker<sup>61</sup> stated that destruction of the supralumbar portion of the spinal cord at any point is followed by disturbances of vesical function, consisting of (1) a stage of retention and (2) a stage of periodic reflex micturition. The average duration of the first stage is about fifty-five days. After some hours or days the urine begins to dribble away, the bladder remaining distended. The second stage develops gradually, and the periodic reflex contractions increase in strength until the bladder is able to empty itself completely. It has been taught that destruction of the lumbar portion of the spinal cord or of the cauda equina is followed by complete paralysis of the bladder, with overflow. However, Thomson-Walker contended that experimental and clinical evidence is to the contrary and that there is the same sequence of events in micturition as occurs in injuries of the supralumbar portion of the spinal cord.

He estimated that in the British forces during the World War the total percentage of deaths due to urinary sepsis following spinal injuries was 80. This was brought about by faulty treatment, namely, intermittent catheterization. This method cannot be too severely condemned.

Thomson-Walker discussed the problem of treatment during the first stage of distention and retention and during the stage of reflex micturition. The methods available during the first stage are: (1) non-interference, (2) expression of the contents of the bladder by pressure

60. Walters, Waltman: An Omental Flap in Transperitoneal Repair of Recurring Vesicovaginal Fistulas, *Surg., Gynec. & Obst.* 64:74-75 (Jan.) 1937.

61. Thomson-Walker, John: The Treatment of the Bladder in Spinal Injuries in War, *Brit. J. Urol.* 9:217-230 (Sept.) 1937.

and massage, (3) the use of an indwelling catheter and (4) early or prophylactic cystotomy.

With the first method, the bladder is allowed to distend without any local interference until overflow takes place, and eventually periodic reflex micturition develops. Although the deleterious effects of the over-distended bladder may have been overemphasized, this method is not recommended for universal adoption because of the possible effects on the musculature of the bladder and future function or on the function and structure of the kidneys; there is also a possibility of rupture of the bladder. The latter has been reported in a number of cases.

The second method consists in gentle but firm compression and massage of the distended bladder through the abdominal wall every four to six hours as soon as possible after injury, with the object of expressing its contents. It should be done early before distention becomes too marked and must be done carefully and skilfully because of the danger of rupturing the bladder. It should not be used when infection has set in.

When the indwelling urethral catheter is used, the bladder is irrigated daily; the catheter is changed twice a week and is removed when reflex micturition develops. This method is certain to produce infection, but if the bladder is kept empty it does not permit reflux and regurgitation to the upper part of the urinary tract. The disadvantages and dangers of this method are: intolerance to the catheter; periurethral infection; the expulsion or plugging of the catheter, permitting the infected bladder to become distended, and the constant supervision necessary to prevent these complications.

Thomson-Walker recommended the fourth method, or early drainage by the suprapubic route, to relieve the distended bladder until reflex urination develops. The objections to early cystotomy have been: (1) difficulty of obtaining a watertight wound, (2) possible interference with the development of automatic function and (3) cystitis, which is inevitable. These objections are groundless, because with ordinary skill the production of a watertight cystotomy wound offers no difficulties. For those to whom it does, the simplified trocar and catheter method of Mothersill and Morson is available.

Although cystitis is inevitable, infection without distention or increased intravesical pressure is not dangerous. Overdistention rather than drainage interferes with development of reflex micturition. Automatic emptying will follow no matter how long the bladder is drained. The suprapubic fistula at this stage heals without difficulty when the tube is removed. Therefore, although in some cases manual expression may be of value, the constant attention and skill necessary over long periods, the failure to empty the bladder completely in some cases and

danger of rupture would indicate that early cystotomy is the method of choice in the first stage.

Thomson-Walker discussed treatment as applied to 100 patients who had survived the wave of surgical sepsis and entered into the second stage, that of the paralyzed bladder. In 69 of these, the bladder was closed, and automaticity had been established. However, complete emptying was seldom observed because of inflammatory infiltration and consequent rigidity of the wall of the bladder from long continued sepsis. In the cases of severe infection suprapubic cystostomy with continuous irrigations with different antiseptics gave the best results. If a suprapubic fistula was present, it was enlarged and the bladder was treated in a similar method. The bladder was kept open in all cases as long as continuous drainage and washings were needed. In the case of moderately infected closed bladders mechanical washing by means of an apparatus constructed on the principles of the automatic flush was carried out for several hours daily. In addition, vaccines and all forms of urinary antiseptics were used, and the patients were encouraged to get up in wheel chairs, which improved their general condition.

*Incontinence.*—Godard<sup>62</sup> reported the successful treatment of urinary incontinence in a girl aged 6 years by the Goebell-Stoeckel procedure. The urinary incontinence had developed in association with spina bifida in the lumbosacral region accompanied by a tumor. When the child was 4 years old an operation had been performed for the spina bifida, and a soft tumor and a lipoma were removed. The incontinence had persisted, together with an insufficient control of the sphincter ani and a talipes varus on the right side. The urine dribbled away drop by drop so incessantly that the child had never experienced the urge to urinate, but on distention of the bladder with 120 cc. of water she was able to feel a slight sensation of pain. Insertion of a sound for its full length as far as it would go elicited a cry, revealing a certain slight conservation of sensitivity on the part of the bladder. A plastic operation on the neck of the bladder of the Goebell-Stoeckel type was carried out, with satisfactory results. Two small musculo-aponeurotic flaps were detached from the right and left rectus muscles, respectively, at the midline and near the umbilicus; left adherent at the bottom to the pubis, they were passed alternately, together with the pyramidalis muscle and its nerve (a branch of the twelfth intercostal nerve), behind the neck of the bladder, like a cravat, and then were brought out in front of the latter and sutured to one another with silk. This made a sort of circular pseudosphincter, suspending the neck of the bladder, the

62. Godard, Henri: Incontinence d'urine par spina bifida lombo-sacr  avec tumeur trait  par l'op ration de Goebell-Stoeckel, *J. d'urolog.* **43**:376-386 (April) 1937.

entire ring being bound to the pubis by the pyramidalis muscle. Suture of the abdominal wall in three planes was somewhat difficult, owing to removal of the central flaps, but was successfully carried out. The first successful attempts at urination were accomplished three weeks later, under the synergistic action of the abdominal muscles and the diaphragm. A course of reeducation was instituted, with the result that at the end of six weeks the child could remain upright for five hours without urinating and could voluntarily void 100 cc. of urine. Continence was considered satisfactory from that time on. Rather extraordinary was the fact that fecal incontinence also practically disappeared, occurring only at the time when the effort to urinate was made. No vesico-ureteral reflux was present, and the capacity of the bladder was 120 cc.

The pure hypogastric Goebell-Stoeckel technic is much better from the point of view of asepsis than the vaginal approach but is a much more delicate operation. With separation of the tissues along the neck of the bladder, hemorrhage along the perivesical plexuses is inevitable, but the procedure was accomplished without evil consequences.

In discussing this case, Gouverneur stated that incontinence of urine in cases of spina bifida is of a special kind, owing to disturbance of endovesical sensibility. It is probable in the present case that a part of the curative action must be credited to the muscular ring formed around a neck of the bladder, followed later by a ring of perivesical sclerosis, but this mechanical action was not the whole, and perhaps not even the essential, correction. It is certain that in dilacerating the perivesical and pericervical nerve plexuses one exerts action on the vesical function, and it is probably in this manner that at the same time that Godard cured his patient of urinary incontinence action was exerted on the plexuses that control the anal function, so that the rectal incontinence also disappeared almost entirely. Amelioration of rectal incontinence is proof that the Goebell-Stoeckel operation finds its true usefulness in the fact that it removes the action of the sympathetic nervous system.

Hill, Barnes and Courville<sup>63</sup> stated that retention of urine with distention of the bladder is a fairly common complication of resection of the rectum for carcinoma. Cellules or small diverticula, ordinarily the result of long continued obstructive or paralytic distention, may appear within two weeks. Urinary retention may be transitory or may be present for days, weeks or even months or, occasionally, may be permanent. The extent and duration of vesical dysfunction depend on the character and extent of damage to the nervous elements.

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63. Hill, M. R.; Barnes, R. W., and Courville, C. B.: Vesical Dysfunction Following Abdominoperineal Resection for Carcinoma of the Rectum, *J. A. M. A.* 109:1184-1188 (Oct. 9) 1937.

The character of the urinary disturbance indicates that the parasympathetic elements are exclusively or predominantly affected. This suggests that the pelvic nerves themselves or the parasympathetic elements in the hypogastric plexuses are the seat of injury. Anatomic dissections make clear the intimate relationship between the pelvic nerves and the hypogastric plexuses and the lower part of the rectum where it penetrates the floor of the pelvis. Injuries to these nervous elements are more likely to take place when the growth involves the upper part of the rectum or the lower part of the sigmoid flexure and when there is widespread involvement of the regional lymph nodes, with fixation to other organs or tissues.

Treatment of retention by an indwelling catheter is indicated as long as there is more than 50 cc. of retained urine. If cystitis develops, which is most likely in a patient who is not catheterized, it should be appropriately treated with lavage of the bladder.

Watkins<sup>64</sup> reported partial retention of urine in 5 persons without obstruction or disease of the nervous system but with a markedly dilated bladder yet with perfect reflex micturition, as characterized by powerful contractions of the detrusor muscle and coordinated reflex relaxation of the urethra. He called the condition "idiopathic dilatation of the bladder" caused by overactive impulses of the sympathetic nervous system and compared it with idiopathic dilatation of the colon, or Hirschsprung's disease.

The condition described could not be classified as atony, because there were powerful contractions of the detrusor muscle. The bladder of 3 of the patients contained from 1,400 to 1,500 cc. of urine; urination proceeded with a good uninterrupted stream, yet there was from 500 to 600 cc. of residual urine. Two of the patients (females) suffered from severe constipation, the bowels acting once a week for 1 patient and once every three weeks for the other. These patients urinated only once in twenty-four hours, and then as much as from 1,200 to 1,700 cc. of urine was passed at a time.

In all of these cases roentgenographic studies of the upper part of the urinary tract showed little damage as a result of back pressure.

Three of the patients underwent presacral neurectomy, with improvement in the function of the bladder and reduction in the amount of residual urine.

*Stone.*—Kretschmer<sup>65</sup> reported a case of xanthine calculi and reviewed the literature on this type of vesical stone. The search revealed

64. Watkins, K. H.: Idiopathic Dilatation of the Bladder, *Brit. J. Urol.* **60**:26-35 (March) 1937.

65. Kretschmer, H. L.: Xanthin Calculi: Report of a Case and a Review of the Literature, *J. Urol.* **38**:183-193 (Aug.) 1937.



the presence of 15 cases on which there were sufficient data for study, and with the case reported by Kretschmer, the total is brought up to 16. The youngest patient was 4 years old, and the oldest was 69. The largest number of cases occurred in persons between the ages of 4 and 15 years. This verifies the statements which have been made that xanthine calculi occur more frequently in young subjects. The sex distribution shows that the males predominate.

Xanthine calculi reported in the literature have varied greatly in size. Langenbeck's specimen was the size of a hen's egg and weighed 338 grains (21,903 mg.). Jaillard's specimen was 2 inches (5 cm.) in length and weighed 350 grains (22,679 mg.); Fleming's specimen was a little larger than a garden pea; the multiple stones in Israel's case totaled 2,300 mg. in weight. The opinion has been expressed by some authors that xanthine calculi are found more frequently in the bladder than at other sites in the urinary tract. In none of the cases in this series was the stone found in the ureter. In 8 cases the stone was found in the bladder; in 3, in the kidney, and in 1, in the urethra. In 4 cases the location was not stated.

In Kretschmer's case roentgenographic examination gave evidence of stone in the bladder, and the review of the cases in the literature showed that positive roentgenographic findings were reported in 3 cases.

A small amount of xanthine is found constantly in the urine and may also occur in the feces with other purine bodies. Urinary calculi composed of xanthine do not seem to present clinical features distinct from other forms of urolithiasis.

Treatment of xanthine calculi does not present any special features distinct from the treatment of urinary lithiasis in general. At present the consensus seems to stress the importance of chemical examination of urinary calculi with the application of the knowledge gained to dietary measures, to prevent the formation of new concretions after operation. In cases of uric acid and xanthine calculi many authors advise a mixed diet with a preponderance of vegetables, fats and carbohydrates—a low protein intake of a purine-free nature.

*Rupture.*—Cahill<sup>66</sup> stated that the incidence of rupture of the bladder is increasing with the increase of automobile accidents. The usual cause of rupture is external traumatism to an overfilled bladder, not uncommonly seen in persons who use alcohol constantly. In an increasing proportion of cases rupture is associated with fracture of the pelvis. Occasionally rupture is secondary to medical manipulations. Intraperitoneal ruptures are more frequent than extraperitoneal ones. The symptoms and signs are shock, abdominal pain and tenderness, with a marked

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66. Cahill, G. F.: Rupture of Bladder and Urethra, *Am. J. Surg.* 36:653-662 (June) 1937.

desire but inability to void. Diagnosis is best made by intravenous pyelography and cystograms showing the diffused dye outside the bladder. This procedure lessens the danger of infection. Rupture of the bladder is a major abdominal catastrophe and requires immediate surgical intervention. Closure of the tear with wide drainage and aspiration is recommended. Complications are shock, hemorrhage and infection.

The mortality has been steadily declining. A review of the literature showed a mortality of 78 per cent in a series of cases reported up to 1907. Since 1929 the mortality as reported at the Squier Clinic of the Columbia-Presbyterian Medical Center, in New York, was 30 per cent. This percentage might be still lower if rupture of the bladder could be isolated from the high percentage of general injuries with which they are associated.

The urethra may be ruptured either from within or from without. Rupture from without is the more usual and is generally due to a fall on the perineum. It frequently occurs with fracture of the pelvis. Symptoms and signs are those of pain, hemorrhage and urinary extravasation. Drainage of the extravasated area followed by repair of the urethral tear gives the best results. Use of an indwelling catheter increases the danger of infection.

#### CANCER OF THE PENIS

Campbell<sup>67</sup> stated that treatment of carcinoma of the penis is guided by the size of the growth, its depth of invasion and the presence of metastasis. Superficial growths less than 2 cm. in diameter and not associated with metastasis will regularly be cured by irradiation. Hopelessly advanced carcinoma of the penis should not be operated on. When there is no apparent metastasis, conservative amputation should be performed. In half of the cases in which metastasis is apparently present in the groin, the suspected lymphadenopathy is purely inflammatory. When metastasis is proved to have occurred, the regional lymphatics should be excised *en masse*. Operations to accomplish this are described.

#### URETHRAL STRICTURE

Mihalovici<sup>68</sup> reported that of a total of 186 persons with filiform stricture treated in the last four years, 68 underwent wide internal urethrotomy, 4 external urethrotomy, 3 resection of the urethra, 3 retrograde catheterization and 3 cystostomy (twice definitive) without any fatal results. He stated that he prefers a modification of the internal procedure with the Maisonneuve urethrotome, with its lateral sections.

67. Campbell, M. F.: Cancer of the Penis: Surgical Treatment, *Am. J. Surg.* 28:55-60 (April) 1935.

68. Mihalovici, I.: Contribution au traitement opératoire et post-opératoire des rétrécissements inflammatoires de l'urètre, *J. d'urol.* 43:439-449 (May) 1937.

In the unmodified Maisonneuve procedure the two sections are not equal in depth, because they are made successively and not simultaneously. In Mihalovici's modification this inequality of the sections is overcome by making them with an instrument that has its two blades of unequal size. This produces two sections of equal depth, at the right and left of the midline. From this point on, the classic procedure is carried out, the conductor being replaced by a mandrin and a sound with a cut end of no. 20, 21 or 22 caliber being introduced. The patient retains this for three days, or in certain cases of callus or multiple strictures, from four to six days. As a rule, four days after the sound is removed dilation with bougies is begun; these are used daily, and the caliber is increased by one size each time. These are generally borne very well, and the maximum size is reached in two weeks. Mihalovici gives the name "period" to the precise interval of time elapsing between passage of the last *béniqué*, or bougie, and the moment when the stricture begins to contract again. This period varies for different strictures, but always remains invariable in one and the same person. The important thing is to establish this period with exactitude. With this end in view, Mihalovici proceeds as follows: After dilation has been done with a sound of the highest caliber, this sound is used again twice, at intervals of three days. After the second sitting, the patient returns in six days, then in twelve, twenty-four and forty-eight days and in two, three and four months and so on, and each time a sound of the caliber which was used last is passed. As soon as it is observed that the last sound is passed only with difficulty, the interval between sittings is diminished. Thus, if after three months sounds of smaller caliber are necessary, the period should be established at two and a half months. The patient must then present himself each time after this exact interval. Some patients have intervals of one, two or three months, but, more frequently, of four, five or six months and even up to one year. They then come to have the bougie passed once each time at the fixed term. Experience acquired during four years has taught that the period, once established, has never varied.

Patients are well satisfied with this improvement over old methods, and as a rule they come exactly on the day that marks their period. The only exceptions are patients with strictures in the anterior third of the penile urethra, who usually suffer rapid recurrence and to whom accordingly there is given a straight *béniqué* of suitable caliber which they pass for themselves at an interval of every two or three days.

If the stricture cannot be controlled or is complicated with fistulas, temporary or definitive cystostomy occasionally has its indications. In all other cases the dilated stricture can be maintained at the same caliber indefinitely.

## TUMOR OF THE SCROTUM

Mintz<sup>69</sup> reported 3 cases of benign tumor of the scrotum—a fibroma of the spermatic cord, a lipoma and a hemangioma of the scrotum. In all 3 cases a preoperative diagnosis of malignant new growth was made, and operation was advised. In 1 case the scrotal tumor could not be palpated as a distinct mass from the testicle, but in the other 2 a definite plane of demarcation could be felt. No history of trauma was obtained in any of the 3 cases. The patients all gave a history of an increasing testicular mass, which was their chief complaint. In no instance did the scrotal tumors transmit light. All 3 patients were successfully operated on; 2 who were traced for several years had no further trouble.

## URINARY CALCULI

Berke<sup>70</sup> sectioned and studied a number of urinary calculi in an effort to determine their structure.

He found that the stones studied had a framework of organic matter which usually consisted of a distinct nucleus and a peripheral structure. The exact nature and distribution of these elements varied with the type of stone. The nucleus consisted of one or several of the following elements: red blood cells, white blood cells and bacteria. The peripheral structure was usually composed of fibrinous matter, arrangement and distribution of which in some of the specimens approached the detail of bone. In other specimens the fibrinous structure was vague and poorly organized. It was probably derived from blood plasma and inflammatory exudate. In some stones varying quantities of uric acid crystals were found. They often appeared as inclusions and bore no distinct relationship to the rest of the structure. However, in others, the fibrinous network was built about the crystals, so that on solution their outlines could be seen in the organic matrix. Inclusions of epithelium were seen, but in no instance were they near the nucleus.

From his observations, Berke concluded that it is apparent that the determining factors in the formation of urinary calculi may be indicated as: inflammatory processes, not necessarily bacterial in origin, furnishing nuclear constituents and fibrin; a suitable crystalloid state of urine (overcharged solution), and retention of the formed nuclear matrix, growth of the calculus usually occurring by accretion and in rare instances by coalescence.

Systemic diseases, especially disturbances of calcium and phosphorus metabolism, pathologic conditions of the bone and foci of infection may be considered predisposing causes of urolithiasis.

69. Mintz, E. R.: Benign Tumors of the Scrotum: Report of Three Cases, New England J. Med. **216**:557-559 (April 1) 1937.

70. Berke, J. D.: Nature of Urinary Calculi, J. Urol. **38**:118-130 (July) 1937.

Holtze<sup>71</sup> discussed the biologic action of the formation of urinary stone. The stability of urine in the urinary tract and its high power of dissolution are guaranteed by the low surface tension between the urine and the intact mucosa, by the presence of hydrotropic substances (urea and hippuric acid) and by content in stable colloids, which absorb comparatively insoluble substances and protect them from precipitation. Urinary calculi contain from 5 to 20 per cent of albumin as a nucleus. It is probable that primarily unstable, mucoid colloids mass together and become encrusted with salts. Urine penetrates in the albuminous mass, leaving the protecting colloids behind and causing the now unprotected, almost insoluble salts to precipitate. Stagnation of urine favors development of stones. With a few exceptions (cystinuria and hypercalcaemia) the concentration of stone-forming salts in the urine is unimportant. Elimination of calcareous salts through the kidneys is parallel with their concentration in the blood and can lead directly to the formation of stone. This occurs most commonly in cases of adenoma of the parathyroid gland.

Experimental and clinical data indicate that it is improbable that vitamin A is of importance in the prevention of stone in a mild climate. Unexplained are the following facts: regional, endemic occurrence of stone, a change in the frequency of stones in the same region over a certain period of time, the hereditary character of the condition, its preference for the male sex and its disappearance among children when they become adults.

Because of the results of experimental work on animals with diets deficient in vitamin A, Higgins<sup>72</sup> placed a selected group of patients who had urinary calculi on a dietary regimen aimed to meet the needs of the particular calculus. Included in this group were: (1) those with bilateral renal calculi on whom operation was not advisable; (2) those with large renal calculus who ordinarily would require nephrectomy; (3) those with small calculus in the renal pelvis which was not producing obstruction, and (4) those with a small calculus in the calix which was not producing obstruction. Treatment was prescribed also when it was desirable (1) to prevent the formation of recurrent calculi, (2) to prevent the formation of calculi in patients who had passed stones at frequent intervals but in whom no calculus could be demonstrated roentgenographically, and (3) to prevent the formation of renal calculi in patients who had orthopedic problems.

It is important that the patient be hospitalized until he is thoroughly familiar with the intricacies of the dietary modifications and until the  $p_H$  of the urine is stabilized at the desired level. In cases of unilateral

71. Holtze, F.: *Biologische Grundlagen der Konkrementbildung*, Ztschr. f. Urol. **31**:334-338, 1937.

72. Higgins, C. C.: *Present Status of Dietary Regimen in the Treatment of Urinary Calculi*, Brit. J. Urol. **9**:36-46 (March) 1937.

stones the  $p_H$  of the urine from each kidney must be obtained, because they can vary widely, and an attempted correction based on the  $p_H$  of the urine in the bladder alone might produce results opposite from those desired.

Eighteen per cent of the bacilli which infect the urinary tract and 40 per cent of the strains of *Staphylococcus albus* split urea, so that regardless of the type of infection it should be determined whether the organism has this power.

The chemical contents of all stones removed surgically or passed spontaneously should be determined as an aid in dietary regulation. The majority of recurrent calculi are composed of calcium phosphate and carbonates. Therefore, shifting of the  $p_H$  level to about 5.2 will prevent precipitation of the phosphates and carbonates and will minimize recurrences. Vitamine A deficiency is more prevalent than is realized. In Higgins' recent series of patients, 63 per cent showed vitamin A deficiency by the biophotometer test. By use of the high vitamin A, acid or alkaline ash diet in addition to the routine urologic armamentarium, Higgins was able to reduce the percentage of recurrent calculi from 16.4 to 4.7 per cent.

In patients with orthopedic conditions who are confined to the recumbent position for long periods of time, urinary calculi occur often and are most frequently composed of calcium phosphate and carbonates. Therefore, in such patients alkaline urinary antiseptic and large amounts of citrus fruits and alkalis are to be avoided. The high vitamin A, acid ash diet will keep the urine at a  $p_H$  unfavorable to formation of calculi.

Seventy-nine of Higgins' patients who had been passing small stones at frequent intervals were completely relieved of their symptoms for over two years by the dietary regimen. In cases of proteus infection the  $p_H$  could not be shifted to the acid side, nor was the infection controlled by dietary measures or by medication by mouth, and the patients continued to pass stones.

In 32 patients in whom a calculus was too large to pass spontaneously, dissolution occurred following dietary treatment in every case. The alkaline ash diet was used in 3 patients with uric acid stones and in 1 with cystine calculi. An acid ash diet caused the dissolution of the phosphate and carbonate stones in the remaining 28 patients.

#### UROGENITAL TUBERCULOSIS

Remete<sup>73</sup> examined material at the Budapest urologic clinic to determine whether Lowenstein's statement that avian tuberculosis played a large part in human urogenital tuberculosis was correct. He confirmed

73. Remete, Tibor: Ueber die Rolle des Geflügeltuberkulosebacillus bei der Tuberkulose der Harn- und Geschlechtsorgane des Menschen, Ztschr. f. urol. Chir. u. Gynäk. 43:202-207, 1937.

the statement of Vorman and Welti, from the urologic clinic in Berne, that they were unable to find a single case in which avian tuberculosis was the cause of urogenital tuberculosis in man. Remete's examination was made on 42 patients and consisted of allergic cutaneous tests, culture and inoculations in guinea pigs and cockerels.

#### ANESTHESIA

Stockwell and Smith<sup>74</sup> related their experiences with pontocain as a spinal anesthetic in 1,000 urological operations. The technic for patients weighing 135 pounds (61 Kg.) or over is as follows:

No preliminary sedatives are given except to children. The authors prefer to administer sedatives, as needed, in the operating room.

For operations on the bladder, pelvis and lower extremities the injections were made at a level of third and fourth lumbar space as follows: for operations of one hour's duration, 1.5 cc. of pontocain hydrochloride, with the aspiration of 0.5 cc. of spinal fluid, and for operations of from one to three hours' duration, from 1.75 to 2 cc. of the drug, with no aspiration of spinal fluid. The average working dose is 1.75 cc. for operations of short duration and 2 cc. for those of long duration. The injection is made at the rate of 2 cc. per minute.

The dose for patients under 135 pounds is figured as 1 cc. of a 1 per cent solution for each 100 pounds (45 Kg.) of body weight and to this is added 0.25 cc. more for prolonged operations. The maximum dose is 2 cc.

Induction is easy and rapid, with an average time of six minutes for the appearance of surgical anesthesia. Perfect anesthesia was obtained in 959 patients and partial anesthesia in 40, of which a few required additional local anesthesia or a few inhalations of nitrous oxide.

Pontocain is slightly more toxic than procaine but when skilfully used no untoward reactions have occurred. Its distinct advantages are smooth onset, perfect anesthesia for two hours and possibly longer, complete absence of depression of the blood pressure, absence of disturbing gastro-intestinal reactions, smooth recovery and total absence of neurologic sequelae. The safety of any spinal anesthesia depends most on the skill and experience of the administrator.

#### HYPOCHLOREMIA AND UREMIA

Török and Babics<sup>75</sup> checked the sodium chloride content of blood and spinal fluid in 17 patients who had true uremia. They found the chlorides either within normal limits or lowered in the blood and spinal

74. Stockwell, A. L., and Smith, C. K.: Pontocaine Spinal Anesthesia in Urology, Surg., Gynec. & Obst. 65:389-392 (Sept.) 1937.

75. Török, Alexander, and Babics, Anton: Beiträge zur Klinik der Hypochlorämie und der echten Urämie, Ztschr. f. Urol. 31:243-249, 1937.

fluid. Results of all other examinations of the blood were consistent with severe uremia. Vomiting and diarrhea were frequent for all patients who had a lowered sodium chloride content.

Török and Babics concluded that loss of salt through profuse diarrhea or frequent vomiting or lack of salt after prolonged use of a salt-free diet can lead to a rise in nonprotein nitrogen, even in persons who have healthy kidneys, similar to that observed in patients with uremia but easily differentiated by the patient's history and by the laboratory findings. Lowering of the freezing point of the blood does not keep pace with the increase in the nonprotein nitrogen. This increase is probably due to the loss of water, which leaves the kidneys with only a small amount of water at their disposal; they are also handicapped by circulatory disturbances due to the lowered blood pressure and are unable to excrete the nitrogenous products of the body's metabolism properly.

Hypochloremia develops even faster when the kidneys are diseased and when the patient is preuremic. In this case even a small loss of water is able to cause serious trouble. Usually in such cases true uremia is present, and hypochloremia is added to the clinical picture in the form of diarrhea, vomiting and anorexia.

#### URINARY ANTISEPSIS

Cook<sup>76</sup> reviewed the results in a group of 500 patients who were treated with mandelic acid. An average daily dose of 12 Gm. of the acid was given to each patient. Most satisfactory results were obtained by continuing this therapy for a period of from six to twelve days. If at the end of this period the urine still contained bacilli, it was found advisable to discontinue treatment for from ten to fourteen days and then subsequently to institute a second course of treatment.

Helmholz and Osterberg have demonstrated experimentally that the usual bacilli found in the urinary tract are destroyed by a 0.5 per cent solution of mandelic acid at a  $p_H$  of 5.5. A lower  $p_H$  will not require such a high concentration of the acid. It is advisable, therefore, to limit the fluid intake during the administration of mandelic acid to 1,200 cc. or less for each twenty-four hours. Mandelic acid in the form of ammonium mandelate will usually maintain the desired level of  $p_H$  without use of secondary acidifying agents. In certain cases, however, it may be necessary to administer ammonium nitrate or chloride or some other acidifying agent at the same time.

Cook reported that in more than 80 per cent of the uncomplicated cases of bacillary infection of the urinary tract the condition responded satisfactorily to this form of treatment. If the infection in the urinary

76. Cook, E. N.: Further Studies on the Use of Mandelic Acid for Infections of the Urinary Tract, Proc. Staff Meet., Mayo Clin. 12:215-217 (April 7) 1937.



tract is complicated by chronic pyelonephritis with cicatricial changes in the pelves or calices, residual urine in the kidney or bladder, chronic prostatitis, stone and tumor, the chances of rendering the urine sterile are definitely reduced. Occasionally symptoms, such as nausea, evanescent microscopic hematuria or hyaline casts in the urine, may accompany the administration of mandelic acid. Some patients have experienced tinnitus and headaches, and rarely certain dermatologic reactions have been observed.

Braasch, in discussing Cook's paper, stated that the clinical evidence of renal irritation resulting from mandelic acid is indefinite. In 2 per cent of the cases red blood cells or a few hyaline casts were found in the urine. Gross hematuria was present in only 2 of the 500 cases. In no instance was there evidence of serious injury to normal kidneys following the administration of mandelic acid. In no case was an increase in the value for blood urea noted following the administration of the acid if the primary renal function was normal. In the presence of damaged kidneys, however, the use of mandelic acid may result in a mild temporary decrease in renal function. Braasch expressed the belief that use of this drug should be contraindicated if there is definite evidence of renal insufficiency.

Helmholz<sup>77</sup> conducted a series of experiments and made a preliminary report on the bactericidal power demonstrated in the urine of a patient who was taking sulfanilamide by mouth. He concluded that many of the organisms that are commonly found in cases of infection of the urinary tract fail to grow in the urine of a patient who has received an appreciable amount of sulfanilamide by mouth. Further reports on this will be forthcoming.

Buchtel and Cook<sup>78</sup> reported their experiences with sulfanilamide in the treatment of more than 200 patients who had infections in the urinary tract. This treatment is considered in general more dangerous than acidification of the urine and administration of mandelic acid, and the latter should therefore be used whenever it will prove effective. Mandelic acid is most successful in uncomplicated cases of bacillary infection and in infections attributable to *Streptococcus faecalis*.

Sulfanilamide appears to be a more potent antiseptic than mandelic acid and when used is effective in an alkaline urine and also at times in the presence of marked renal insufficiency.

Coccic infections do not respond as well to sulfanilamide as do bacillary infections; this is especially true of infections due to *Str. faecalis*. The authors present an analysis of results in the following conditions

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77. Helmholz, H. F.: The Bactericidal Power of the Urine After the Administration of Prontylin by Mouth, *Proc. Staff Meet., Mayo Clin.* **12**:244-245 (April 21) 1937.

78. Buchtel, H. A., and Cook, E. N.: The Use of Sulfanilamide in Treatment of Urinary Infections, *Proc. Staff Meet., Mayo Clin.* **12**:444-446 (July 14) 1937.

in which sulfanilamide has proved greatly superior to any other anti-septic: prostatitis, urinary infection associated with prostatitis and gonorrhea.

So far, 93 patients with infections of this type have been treated. Eight were unable to take adequate doses of the drug, and the therapeutic results in these cases were classed as failures. There were 17 patients with prostatitis unassociated with urinary infection; after one week's treatment some reduction of the prostatitis was obtained in 7 and marked reduction of the prostatitis in 9. One patient showed no improvement while taking an adequate dose. The bacteriologic composition of the prostatic secretion of the patients who responded well to treatment was no different from that of the prostatic secretion of the patients who did not respond to therapy. Patients who had associated nonspecific urethral discharge were also relieved.

There were 45 patients with prostatitis and an associated urinary infection; in 33 a bacillary infection was present, and in 12, a coccic infection. Good results were obtained in 30 of the former and in 6 of the latter, and there was a significant reduction of the amount of prostatitis in 62 per cent of the group. The patients with proteus infections responded as well as those with infections attributable to other bacilli. Eleven of those with proteus infection had taken mandelic acid previously, 1 of whom also failed to obtain relief from the use of sulfanilamide. Buchtel and Cook have previously emphasized the prognostic value of prostatic cultures in the treatment of bacillary infection. Culture of prostatic secretion will be found to be positive in 50 per cent of cases of prostatitis in which urine is sterilized by mandelic acid. In the reported cases in which sulfanilamide was used, 24 cultures of prostatic secretion were made and only 1 was positive.

Thirty-one patients had gonorrhea; 21 were men and 10 were women. Two men still had symptoms after one week of treatment, and the results of these treatments were classed as failures. Two women still had positive cultures at the conclusion of the treatment. There were 2 cases of epididymitis, 1 of arthritis and 1 of acute salpingitis, in all of which good response occurred. Cook and Buchtel have not as yet seen any recurrences following the cessation of treatment, in spite of repeated examinations. This may be due to the method of giving the drug.

This has been a most difficult drug for which to develop a standard scheme of dosage, as individual tolerance varies immensely. Ordinarily Cook and Buchtel start with an initial dose of 60 or 80 grains (4 or 5.3 Gm.) daily. This is continued for one or two days and then is reduced. After another two days the patient is placed on a maintenance dose, which is usually 40 grains (2.6 Gm.) daily, for a maximal period of ten days. In the cases of gonorrhea, once clinical cure is accomplished a dose of 20 grains (1.3 Gm.) daily is continued for from ten to fourteen days.

The authors' results from this dose of sulfanilamide have been so superior to those obtained by a constant small daily dose that it seems justified, in spite of the fact that 15 per cent of patients cannot take it. Some of these patients can start with a small dose and gradually work up to a larger one; others will obtain good results on a small daily dose; the remainder, about 10 per cent, cannot take the drug at all. It was early noticed that less sulfanilamide could be taken by an ambulatory patient than by one who is at rest in bed. Ordinarily, only the first two to three days will have to be spent in bed; after that, the dose can be reduced. Cook and Buchtel recommended this procedure when the patient is doing poorly.

Reactions are common and may prove very serious. Lassitude, dizziness and slight headache occur almost invariably. If these are relieved by rest, the dose need not be reduced. More severe reactions necessitate reduction of the dose or cessation of the drug. To continue large doses in the face of severe headache, fever, gastro-intestinal upsets, mild cyanosis, paresthesia or other reactions is inviting disaster. If any of these symptoms are severe or if cutaneous reactions occur, administration of the drug should be permanently stopped.

It is unnecessary to produce even the mildest reaction to obtain good results. As a general rule, patients taking the largest dose will show the best results. Men can take larger doses of sulfanilamide than women, and the young, more than the aged. With increasing experience, serious reactions become increasingly rare.

#### DIURETICS

Keith<sup>79</sup> stated that the diuretic action of mercurial compounds depends on the available amount of mercury present. Organic mercurial compounds produce the most marked immediate diuresis. The action is chiefly on the kidneys. Diuresis which follows the administration of mercurial compounds is usually more satisfactory than that which follows the use of digitalis or caffeine compounds, even in cases of cardiac disease. The usual procedure is to inject intravenously 0.5 cc. of a given organic compound as an initial trial dose. If no toxic effects are evident, 2 cc. is injected every three or four days as long as there is distinct diuretic response.

Of the acid-producing salts, ammonium nitrate has the most marked diuretic effect and causes less digestive disturbance. The diuretic effects of the xanthine derivatives are not so great, so rapid or so uniform as are the effects of organic mercurial compounds. The combined use of diuretics has a distinct place in present day treatment of dropsy. The

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79. Keith, N. M.: The Action and Use of Diuretics with Especial Reference to Mercurial Compounds, *J. A. M. A.* **107**:2047-2051 (Dec. 19) 1936.

best results are obtained when the acid-producing salts or such salts as potassium nitrate and potassium chloride are administered before the organic mercurial compound is injected intravenously.

#### GYNECOLOGIC DISORDERS AND DISTURBANCES OF THE URINARY TRACT

The incidence of secondary changes in the upper part of the urinary tract in association with various types of gynecologic disorders is high. Kretschmer and Kanter<sup>80</sup> found evidence of changes in the upper part of the urinary tract in 64.7 per cent of 51 cases. Changes were found in 65.7 per cent of the cases of fibroid tumor, in 81.9 per cent of the cases of ovarian cyst and in 25 per cent of the cases of prolapses; in the 1 case of tubo-ovarian abscess there was no change in the upper part of the urinary tract. Failure to appreciate the frequency with which these lesions occur is due to the fact that there have been no routine preoperative studies in cases in which urinary symptoms and urinary signs are not present.

After an appropriate surgical procedure, a return to normal took place in 72.5 per cent of cases. Subsequent pyelograms should be carried out in all cases in which recovery has not occurred at the time the patient is discharged from the hospital.

Äcs<sup>81</sup> emphasized the importance of the changes in the urinary tract caused by myomas of the uterus. He found marked urologic changes in 20 per cent of his cases. These changes are caused by disturbances in the circulation of the pelvis, making the bladder and the upper part of the urinary tract easily accessible to infection. In a few cases the growth, by pressure on the urethra, the bladder or the ureters, causes dilation and urinary back pressure. Myomas, even if they are small, should be surgically removed, if they are the cause of troubles in the urinary tract. Removal of the growth causes prompt recovery from the urinary symptoms and prevents recurrence or inflammatory changes.

#### UROGRAPHY

Braasch and McDaniel<sup>82</sup> stated that apparent filling defects in the outline of the renal pelvis, renal calices and ureter are frequently seen in the course of routine excretory urography. Many of these have no

80. Kretschmer, H. L., and Kanter, A. E.: Effect of Certain Gynecologic Lesions on the Upper Urinary Tract: A Pyelographic Study, *J. A. M. A.* **109**:1097-1100 (Oct. 2) 1937.

81. Äcs, Niklaus: Durch Myome verursachte Veränderungen der Harnwege, *Ztschr. f. urol. Chir. u. Gynäk.* **43**:237-247, 1937.

82. Braasch, W. F., and McDaniel, J. Z.: Significance of Filling Defects in the Urogram, *Tr. Am. A. Genito-Urin. Surgeons* **29**:305-312, 1936.

clinical significance. In fact, complete visualization of the renal calices is not obtained in most cases. In some cases the filling defect may be visible in the first urogram but may disappear in subsequent urograms, or vice versa. In many excretory urograms peristalsis is so active that visualization of the renal calices or pelvis may be extremely fragmentary, which in some cases may be explained by some form of imbalance in sympathetic innervation. Further difficulty in interpretation may be caused by overlying intestinal shadows, which often simulate filling defects in the renal pelvis. That these various apparent filling defects are frequently without anatomic basis is shown by their subsequent disappearance in a retrograde urogram. On the other hand, filling defects observed in the excretory urogram, when confined to the renal pelvis or to one or two renal calices and when they persist in the retrograde urogram, may be the only urographic evidence of an organic lesion and should be regarded as important evidence. Fragmentary visualization of the renal calices in the excretory urogram may disguise an actual filling defect, and if a neoplasm is suspected, a retrograde urogram should always be made.

Filling defects of organic origin which involve the renal pelvis, renal calices and the ureter are caused by a great variety of conditions, including tumor, blood clots, lithiasis, cicatricial changes, congenital deformity, postoperative deformity, granulomas, pyelo-ureteritis cystica, air bubbles, reflex spasm and tuberculosis.

Braasch and McDaniel discussed renal tumor as a common cause of filling defects in the outline of the renal pelvis and the renal calices, which may be visualized in the urogram. Although a cortical tumor usually affects the outline of the calices more than that of the renal pelvis, it may invade the pelvic lumen to a variable degree and occasionally will obliterate it. A filling defect caused by papillary epithelioma of the renal pelvis is usually confined to the renal pelvis itself, and it is often accompanied by a variable degree of pyelectasis, which involves all the calices as well as the pelvis.

Clotted blood is a common cause of a filling defect in the renal pelvis or in the ureter. This may be confined to a small portion of the pelvis or ureter, or it may obliterate their lumen entirely. When blood clots become large and organized and cause persistent urinary obstruction, temporary dilatation of the pelvis and calices may result. Blood clots usually will cause an irregular filling defect, and the shadow produced by these clots often contains areas of variable density, which suggest vacuoles. Such filling defects may be confused easily with those caused by papillary epithelioma of the renal pelvis, which sometimes causes a similar deformity. In order to exclude the possibility that filling defects observed in the urogram might be the result of recent hematuria, urogra-

phy should be repeated at the end of a week or two, that is, after the blood clots have had time to disappear. Clots which persist after hematuria caused by a condition such as pyelitis or essential hematuria have been known to cause considerable confusion in diagnosis. Blood clots in the ureter may prevent visualization of the pelvis of the kidney in the excretory urogram.

Braasch and McDaniel mentioned that as a result of ureteral catheterization and injection of fluids into the renal pelvis a bubble of air sometimes remains, which may cause a shadow suggestive of a filling defect. Air bubbles in the renal pelvis have been described in cases in which there has not been any previous instrumentation.

An apparent filling defect in the urogram may be caused by overlapping outlines of the major calices in a bifid pelvis. The intervening space between the calices may produce a shadow suggestive of a filling defect. When in doubt in cases of this kind, another urogram should always be made at a different angle.

Filling defects in the renal pelvis are often observed in cases of renal lithiasis. The urogram is of particular clinical value in exact localization of the stone and in the identification of nonopaque renal calculi.

A primary tumor of the ureter usually causes a filling defect and a localized narrowing in the ureteral lumen, with a variable degree of pyelo-ureterectasis above or around the tumor. When the tumor is small, the deformity may be difficult to recognize. Since visualization of the ureter is often inexact in the excretory urogram, it is advisable to make a retrograde urogram in every case in which a diagnosis of ureteral neoplasm should be excluded. Ureteritis cystica, when advanced, and a granuloma may cause a filling defect in the ureteral lumen and may produce a similar deformity. The latter, if large, may be confused easily with a neoplasm. Blood clots in the ureter may cause similar confusion. Acute angulation of the ureter as the result of ureterectasis and chronic ureteritis may also cause apparent filling defects in the ureterogram. The passage of bulbous bougies usually will not reveal any actual constriction.

Although visualization of the bladder is more or less a by-product of the excretory urogram, it frequently affords data of unexpected importance. The amount and density of iodine excreted into the bladder vary in different persons. It will be sufficient in many cases to visualize any gross defect in the outline of the bladder. On several occasions filling defects in the excretory cystogram have suggested the presence of neoplasm which was not previously suspected. In others, the extent of the tumor could be inferred better than in any other way. On the other hand, incomplete filling of the bladder may give an erroneous impression of a filling defect, and other corroboratory data are usually necessary.

## FEVER THERAPY

Desjardins, Popp and Stuhler<sup>83</sup> reviewed the results obtained by fever therapy in cases of gonococcic infection of the urethra, epididymis, prostate gland, uterus, fallopian tubes and articulations from the time this form of treatment was started until July 1, 1936. During this interval various changes in the technic of treatment have been made. By these improvements in treatment, cure was effected in 92 per cent of the cases that were reported in 1936. Between Dec. 1, 1933, and July 1, 1936, 210 patients suffering from acute or chronic gonorrheal infection were treated with fever therapy. Of this number, 41 did not complete their treatment, or treatment had to be abandoned for various reasons. This group of patients was excluded from consideration. Of the 169 patients who had a complete course of treatment, 152, or 90 per cent, were cured and have not had any further physical difficulties caused by the gonococcus. Seventeen patients, or 10 per cent, were not completely cured, but their condition was improved in varying degrees. Details regarding the technic of treatment, the type of patients subjected to treatment, the criteria for cure, the factors of importance in reducing the risk of treatment to a minimum and the symptoms resulting from fever therapy are discussed.

According to the authors, it would be contrary to fact to say that fever therapy is entirely devoid of danger. At the time of their report, 516 patients had been treated with fever therapy for various conditions, and these patients had received approximately 2,580 sessions of treatment. Of this number, 1 patient died under treatment.

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83. Desjardins, A. U.; Popp, W. C., and Stuhler, L. G.: Fever Therapy for Gonococcic Infection, *M. Clin. North America* 21:885-891 (May) 1937.

## ACUTE ILIAC ADENITIS

### REPORT OF EIGHTEEN CASES

F. GLENN IRWIN, M.D.

SAN JUAN, PUERTO RICO

Acute iliac adenitis, or inflammation in the iliac lymph glands, presents a clinical picture which is not as uncommon as its lack of recognition would indicate. The disease usually occurs in children or in young adults. It is characterized by a history of cutaneous infection or of trauma of the lower extremity or abdomen which precedes by two or three weeks the appearance of a large, hard, tender, fixed mass in the iliac fossa. There are pain, fever, leukocytosis and spasm of the psoas muscle producing flexion deformity of the thigh.

The purpose of this study is (1) to review the scanty literature, (2) to present the report of a series of 18 cases and (3) to give a clear and comprehensive description of this seldom correctly diagnosed clinical entity.

### REVIEW OF THE LITERATURE

Abrille<sup>1</sup> in 1854 reported 8 cases of suppuration in the retroperitoneal tissues. At that time few pathologists had given the subject serious attention. He divided infection of the retroperitoneal space according to frequency into (1) abscess in the iliac fossa, (2) abscess behind the pelvic peritoneum and (3) perinephritic abscess. He had no knowledge of the cause, considering the condition of traumatic or of idiopathic origin. In 1903 Pegram<sup>2</sup> described 2 cases of iliac adenitis as illustrating possible errors in the diagnosis of disease of the hip joint. The two cases he reported were those of a boy of 3 years and a girl of 6 years. Both had pain, fever, leukocytosis, flexion deformity of the thigh and tumor in the left iliac fossa. Both were operated on, and pus was encountered in the iliac glands of both. His is the first

From the Surgical Service, Presbyterian Hospital.

1. Abrille, C.: Retroperitoneal Abscess, *Gaz. d. hôp.* 27:218, 1854.

2. Pegram, J. C.: Report of Two Cases of Suppuration of Retromesenteric Lymph Nodes, *Tr. Rhode Island M. Soc.* 6:643, 1903.



complete description of the syndrome. Hamann<sup>3</sup> in 1907 reported 3 cases, the patients being respectively 13, 5 and 2 years of age, in which suppuration started primarily in the iliac glands, giving the typical picture of fever, flexed thigh and mass in the iliac fossa. Huggins<sup>4</sup> reviewed the literature up to 1911 on suppuration in the retroperitoneal space. Of the 8 cases he reported, 2 were instances of the iliac variety.

The syndrome of iliac adenitis is apparently well known in South America. From Argentina, Rivarola<sup>5</sup> in 1924 presented a clear and accurate description of the disease. Lugones<sup>6</sup> in 1926 observed 3 cases in which the condition occurred in children and was metastatic following bronchopneumonia. Coutts<sup>7</sup> in 1927, from Chile, reported 4 cases, in all of which the disease was traceable to preceding infection in the urethra, the prostate or the rectum. Bailey<sup>8</sup> in 1930 published reports of 7 cases, and in 1935 he had observed 5 more. Hyman<sup>9</sup> in 1930 was able to collect data on 21 patients with the condition who had been admitted to Mount Sinai Hospital, New York. Both Bailey<sup>8</sup> and Hyman<sup>9</sup> commented on the scarcity of publications on this subject. Largos García<sup>10</sup> in 1931 reviewed the South American literature, presented 38 cases of his own and admirably summarized the clinical picture. Barbarousse and del Campo<sup>11</sup> in 1933 published in detail the reports of 10 cases from Uruguay. Bose<sup>12</sup> in 1934 recorded 2 cases in which the condition simulated appendicitis. To the records of the 92 cases just mentioned I add the 18 following.

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3. Hamann, C. A.: Suppuration in the Retroperitoneal Glands, *Cleveland M. J.* **6**:399, 1907.

4. Huggins, R. H.: Suppuration in the Retroperitoneal Space, *Surg., Gynec. & Obst.* **12**:276 (Feb.) 1911.

5. Rivarola, R. A.: Adenitis iliacas agudas, *Bol. y trab. de la Soc. de cir. de Buenos Aires* **8**:195, 1924.

6. Lugones, C.: Adenitis agudas de los ganglios iliacos, *Rev. méd. latino-am.* **11**:124 (Jan.) 1926.

7. Coutts, W. E.: Acute Inflammation of Deep Iliac Lymph Nodes, *Rev. Soc. urol. de Chile* **9**:268 (Nov.) 1926.

8. Bailey, H.: Suppurating Deep Iliac Glands, *Practitioner* **124**:223 (Feb.) 1930.

9. Hyman, A.: Suppurative Retroperitoneal Pelvic Lymphadenitis, *Ann. Surg.* **91**:718 (May) 1930.

10. Largos García, A.: La adenitis iliaca aguda, *Semana méd.* **2**:1160 (Oct. 8) 1931.

11. Del Campo, R. M., and Barbarousse, C. M.: Las adenitis iliacas agudas en el niño, *Arch. de pediat. d. Uruguay* **4**:43 (Feb.) 1933.

12. Bose, M.: Lymphadenitis of the Retroperitoneal Glands Simulating Appendicitis, *Indian M. Gaz.* **69**:579 (Oct.) 1934.

## REPORT OF CASES

CASE 1.—N. D., a boy aged 7 years, was admitted to the hospital in March 1934, with a history of pain in the right lower quadrant of the abdomen, fever, anorexia and inability to straighten the right leg of thirty days' duration. He had had frequent cutaneous infections for three years. Clinical findings were: temperature 101 F., tachycardia, old impetiginous lesions of the extremities and rigid flexion deformity of the right thigh. The abdomen was soft, allowing a large, hard, tender, fixed mass in the right iliac fossa to be outlined with ease. The tumor extended from the inguinal ligament 7 cm. upward and medially. The inner superior border was rounded and dipped deeply into the abdomen. Results of tuberculin tests and of serologic tests for syphilis were negative; the white cell count was 21,600, and there was mild anemia. Roentgenograms of the spine, pelvis and hip joint showed normal structures. With continuous ice compresses applied over the tumor, forced fluids and general nursing care the fever gradually subsided and the mass and psoas spasm slowly disappeared. The patient was discharged "well" thirty days after admission.

CASE 2.—M. V., a boy aged 10 years, entered the hospital in 1927 complaining of fever and pain in the left side of the abdomen of twenty-seven days' duration. A hard, tender, sharply outlined mass was present deep in the left iliac fossa, extending 5 cm. above the inguinal ligament. All movements of the hip joint were freely elicited except extension. A count of 30,000 leukocytes was observed, and there was moderate secondary anemia. At operation a small abscess was found in the thick-walled tumor and was drained. *Staphylococcus aureus haemolyticus* was grown from the pus obtained. A section of the wall of the tumor removed for pathologic study was described as retroperitoneal tissue infiltrated with polymorphonuclear leukocytes and round cells. Recovery was uneventful.

CASE 3.—P. L., a boy aged 13, was first admitted to the hospital in November 1932, with a history of fever, pain in the right side and inability to extend the right thigh during the past thirty days. He had sustained an injury to the right groin three years previously, when he was kicked by a horse. He had had repeated cutaneous infections of the feet and legs. His parents had noticed a lump in the right side of the abdomen, which had been slowly increasing in size during the last thirty days prior to admission. Clinical findings of importance were pallor, a temperature of 101 F. and a tender, fixed firm mass in the right iliac fossa. The right thigh was held rigidly flexed on the abdomen and could not be extended. Many scars of old impetiginous lesions were present on the lower extremities. Laboratory examinations revealed: red cell count, 1,440,000; hemoglobin, 38 per cent; white cell count, 18,000; result of serologic test for syphilis, negative. Many hookworm ova were present in the stools. Roentgenograms of the spine and pelvis showed them to be normal. With ice compresses over the tumor, hookworm treatment and correction of anemia the mass slowly disappeared, and the patient was discharged well two months after admission. He returned in August 1935, three years later, with a history for the past eleven days of pain, fever and reappearance of the mass. He had been well during the interim. Clinical findings were identical with those obtained at the first admission. A hard, tender mass again occupied the right iliac fossa (fig. 1). No improvement having been obtained by medical treatment, an incision was made over the mass and the peritoneal cavity was entered. A large hard tumor 5 cm. in diameter filled the right iliac fossa completely. The tumor grossly resembled a sarcoma. It was extraperitonealized and incised. A small quantity of thick green pus was encountered at the center of the abscess, which produced on culture a hemolytic *staphylococcus*. A fragment

of the wall of the tumor removed for biopsy was described by the pathologist as follows: There was homogeneous grayish white tissue which showed numerous closely packed, medium-sized polygonal cells with pale, vacuolated, acidophilic cytoplasm and prominent oval nuclei. Local hemorrhage and numerous foci of infiltration by polymorphonuclear leukocytes were present. The diagnosis was chronic inflammatory changes (fig. 2). With drainage of the abscess convalescence was rapid, and the boy was discharged twenty days after admission.

CASE 4.—L. A., a girl aged 8 years, was admitted to the hospital in January 1935, complaining of pain in the right lower quadrant of the abdomen, fever and inability to extend the right thigh during the past five days. She had had a chronic vaginal discharge since infancy. Physical examination disclosed a soft abdomen in which could be felt a globular hard, fixed, tender mass, 6 cm. in

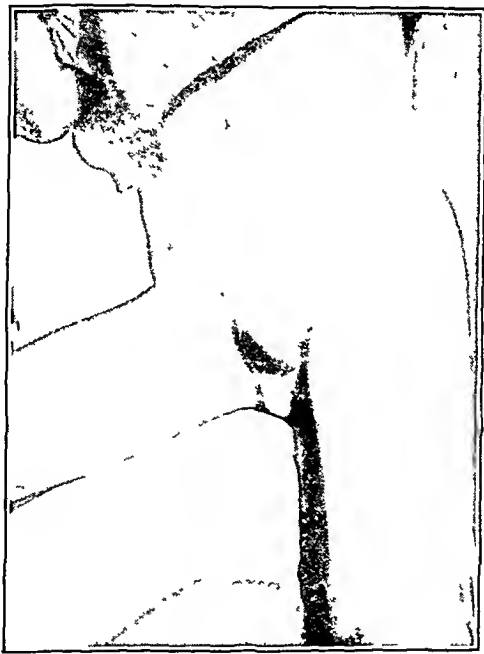


Fig. 1 (case 3).—Photograph illustrating spasm of the psoas muscle with flexion of the right thigh. The tumor is visible in the right iliac fossa (upper margin outlined with mercurochrome).

diameter, occupying the right iliac fossa. The right thigh was flexed on the abdomen. A leukocyte count of 21,900, an erythrocyte count of 3,200,000 (indicating secondary anemia) and a hemoglobin content of 59 per cent were observed. A mixed bacterial flora was present in the vaginal smear. No improvement was obtained with local heat. At operation an incision was made above and parallel to the inguinal ligament. A small abscess was found in the iliac glands, and was drained. *Staph. aureus haemolyticus* was grown from the pus. Recovery was uneventful.

CASE 5.—S. O., a boy aged 4 years, entered the hospital in September 1925. He had had a chronic infection of the upper respiratory tract for two months and pain in the right lower quadrant of the abdomen for two weeks. He had fever and had vomited. Physical examination revealed a feverish sick child with the

right thigh rigidly flexed on the abdomen. A mass was visible in the right iliac fossa, which measured 5 cm. at its greatest diameter. Secondary anemia and a leukocyte count of 20,000 were observed. Roentgenograms of the spine, the pelvis and the hip joints showed no abnormal changes. Incision over the mass disclosed a large, hard tumor with a small abscess cavity at its center. Culture of the pus produced a pneumococcus. Convalescence with drainage was rapid. The patient was discharged well thirty-two days after admission.

The remaining 13 cases are presented in tabular form.



Fig. 2 (case 3).—High power magnification showing a section through the wall of the abscess and the hyperplastic character of the retroperitoneal tissue.

#### COMMENT

From the histories and clinical findings in the cases reported, certain characteristics of acute iliac adenitis are seen to be present constantly enough to form a syndrome. The vagueness of the symptoms at onset and their resemblance to those of acute appendicitis, disease of the hip joint, osteomyelitis of the head of the femur and abscess of the psoas muscle account for the infrequency of correct diagnosis of the condition.

The abscess occurs in the external iliac lymph glands of either side. These glands are divided into external, middle and internal chains. The external chain is comprised of three or four glands which show a tendency to insinuate themselves between the internal border of the

*Thirteen Additional Cases of Acute Iliac Adenitis*

Case No.	Age, Sex	Symptoms	Duration	Predisposing Cause	Clinical Findings	Laboratory Data	Operation	Bacteriologic Findings	Result
6	10 M	Pain in left lower quadrant; temperature 103 F.	12 days	Pyogenic infection of skin of leg	Psoas muscle spasm on left side; mass in left iliac fossa	R.B.C. 3,500,000; hemoglobin 50%; W.B.C. 12,000; whip ova	Drainage of retro-peritoneal iliac abscess	Culture not made	Discharged well in 21 days
7	2 F	Pain in abdomen; temperature 102 F.	11 days	Old cutaneous infection on right knee	Round tender mass in right iliac fossa; psoas muscle spasm	R.B.C. 3,300,000; hemoglobin 80%; W.B.C. 15,950; ascaris ova	Drainage of retro-peritoneal abscess 3 cm. in diameter in iliac fossa	Staph. aureus haemolyticus	Recovery in 35 days
8	3 F	Pain in left lower quadrant of abdomen; temperature 101 F.	14 days	Not known	Hard tumor in left iliac fossa; psoas muscle spasm on left side	R.B.C. 3,200,000; hemoglobin 50%; W.B.C. 13,800; Kahn test negative	None (medical treatment)	.....	Recovery in 24 days; disappearance of mass
9	21 M	Pain in left lower quadrant of abdomen; temperature 101 F.	30 days	Cutaneous infection on left knee	Psoas muscle spasm on left side; mass in left iliac fossa	R.B.C. 2,500,000; hemoglobin 45%; W.B.C. 22,000	Incision and drainage of large iliac abscess	Staph. aureus haemolyticus	Recovery in 18 days
10	5 F	Pain in right side; temperature 102 F.; anorexia; vomiting	7 days	Not known	Mass in right lower quadrant; psoas muscle spasm	Hemoglobin 75%; hook ova in stools	Drainage of small abscess in iliac glands	Culture not made	Recovery in 14 days
11	16 M	Temperature 104 F.; abdominal pain	10 days	Not known	Psoas muscle spasm; mass in right iliac fossa	W.B.C. 31,500	Drainage of iliac abscess	Culture not made	Recovery in 29 days
12	2½ M	Pain in abdomen; temperature 101 F.; inability to extend left thigh	21 days	Trauma; fall with blow on left buttock	Tumor in left lower quadrant of abdomen; psoas muscle spasm on left side	R.B.C. 4,100,000; hemoglobin 70%; W.B.C. 9,400	Drainage of iliac abscess; 100 cc. thick pus	No growth	Uneventful recovery

13	7 M	Pain in left side; temperature 101 F.	12 days	Pain in left leg 6 months previously	Mass in left lower quadrant of abdomen; psaos muscle spasm	R.B.C. 3,860,000; hemoglobin 60%; W.B.C. 17,800; tuberculin test negative	None (medical treatment)	.....	Recovery in 14 days; disappearance of mass
14	25 M	Pain in right side; fever, malaise, anorexia	25 days	Not known	Painful; psaos muscle spasm on right side; mass above Ponsart's ligament	R.B.C. 3,200,000; hemoglobin 70%; W.B.C. 12,000	Incision over mass; drainage of thick-walled fine abscess (appendix normal)	Culture not made	Recovery in 14 days
15	2 F	Swelling, pain and tenderness in right lower quadrant of abdomen	30 days	Impetiginous lesions on lower part of abdomen and on legs	Right thigh flexed; mass in right iliac fossa	R.B.C. 3,500,000; hemoglobin 50%; W.B.C. 18,000; tuberculin test negative	None (medical treatment)	Staph. aureus hemolyticus from cutaneous lesion	Recovery in 21 days; disappearance of mass
16	18 M	Dull pain in left lower quadrant of abdomen; inability to extend left thigh; fever	21 days	Old infected septic lesions of lower part of abdomen	Psaos muscle spasm on left side; mass in left iliac fossa	R.B.C. 3,450,000; hemoglobin 62%; W.B.C. 23,600; hook ova	Incision and drainage of retro- peritoneal tumor, sarcoma-like, in left iliac fossa	Staph. aureus hemolyticus	Prompt recovery
17	7 M	Inability to extend right leg; pain in right lower quadrant of abdomen; fever	21 days	Pyogenic infection of right foot 3 weeks previously	Flexion deformity of right thigh; mass above inguinal ligament	R.B.C. 3,750,000; hemoglobin 60%; W.B.C. 16,200; hook ova	None (medical treatment)	.....	Recovery; disappearance of mass
18	8 M	Fever; pain in left iliac fossa; flexion of left thigh on abdomen	22 days	Pyogenic infection of skin of legs	Visible mass in left iliac region; psaos muscle spasm on left side	R.B.C. 2,250,000; hemoglobin 13%; W.B.C. 9,100; hook ova; tuberculin test negative	None (medical treatment)	.....	Recovery in 32 days; disappearance of mass

psoas muscle and the external iliac artery. The lowest gland of this chain, located behind the crural arch, is usually of fair size and is called the retrocrural gland (fig. 3). It is the gland most often involved. The majority of lymphatics which eventually terminate in the external iliac chain end in this gland. It receives efferent lymphatics from the superficial and deep inguinal glands draining the buttocks, the perineum and the lower extremity, and some deep lymphatics from the subumbilical portion of the abdominal wall (Poirier, Cuneo and Delamere<sup>13</sup>).

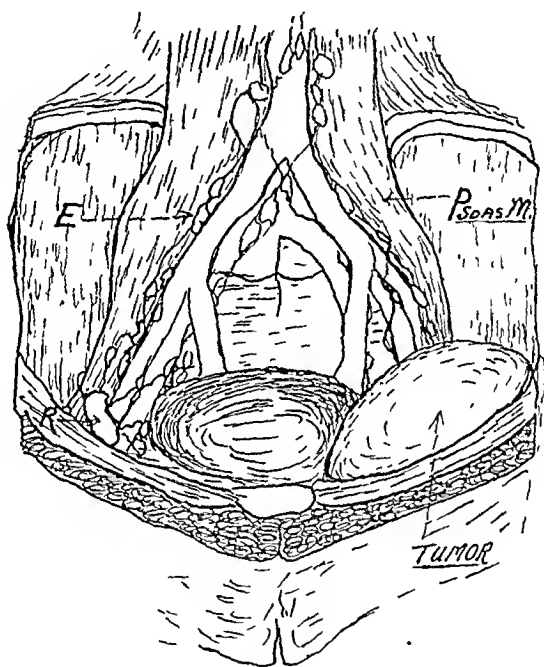


Fig 3.—A schematic representation of the pelvic lymphatic glands and the usual location of the inflammatory tumor. *E* indicates external iliac lymph glands, and *R*, the retrocrural gland.

Predominantly, iliac adenitis is a disease of childhood, especially in Latin and tropical countries, where the children of the poor wear no shoes and cutaneous infections are common. In the 92 cases mentioned in the literature, 76 patients were children or young adults. The average age in my own series was 9 years. The disease is more common in boys than in girls, the proportion being 63 boys to 29 girls in the cases reviewed and 13 boys to 5 girls in my own series. Undoubtedly the reason for this is that trauma and infection are more common

13. Poirier, P.; Cuneo, B., and Delamere, G.: *The Lymphatics*, Chicago, W. T. Keener Co., 1904.

in boys than in girls. The two sides of the body are equally involved, although apparently the condition is never bilateral.

Predisposing causes are (1) infection of the cutaneous areas drained by the iliac glands, (2) trauma, (3) blood-borne (metastatic) infection and (4) idiopathic factors. In the majority of cases some trifling infection of the skin of the lower part of the abdomen, the legs, the buttocks or the perineum can be found. In 11 of my cases evidences of old impetigo or of staphylococcic infection of one of these regions were present. Both Bailey<sup>8</sup> and Lugones<sup>6</sup> mentioned that the inguinal glands are usually not involved. In only 1 of this series of cases were they palpably enlarged. Explanation of this peculiar fact must lie in the developmental anatomy of the lymphatics, since inguinal adenitis is common in the adult.

A history of trauma from a fall or of a blow to the lower part of the abdomen can often be obtained (case 3). That the condition can be metastatic in origin was first noticed by Lugones,<sup>6</sup> who reported 3 cases in which it followed pneumonia. Lagos-García included 3 patients in whom iliac adenitis developed after typhoid fever, scarlet fever and measles, respectively. Hyman<sup>9</sup> included 4 cases of blood-borne infection following otitis media, boils and pneumonia.

In my series 1 case (case 5) is representative of this group. In many cases the predisposing cause remains obscure. It is possible for the local lesion to heal before the patient is aware of the developing adenitis. In this series of 18 cases, examination of 4 of the patients gave no clue to the predisposing cause.

The average duration of symptoms before medical attention was sought was seventeen days. Pain in the iliac fossa, the lower part of the abdomen or the groin is the predominant symptom. It is accompanied by fever, which is of low grade at first, the temperature gradually rising higher and higher as the suppuration advances. Most patients complain of inability to straighten the flexed thigh. Vomiting is not unusual. Pallor, malaise and anorexia are present. Physical examination discloses spasm of the psoas muscle with flexion deformity of the thigh. A mass is always present occupying the iliac fossa and can often be felt through the rectum. The leukocyte count is from 15,000 to 35,000. Mild anemia is present. Differential diagnosis is not difficult if the syndrome is known. The slow onset and long duration of symptoms, the absence of signs of peritonitis and the presence of the tumor differentiate the condition from appendical abscess. The free motion of the hip joint with the exception of extension rules out the possibility of suppurative arthritis. Roentgenograms of the spine and pelvis and negative reactions to tuberculin tests exclude the possibility of tuberculosis of the bone.



## TREATMENT

Conservative treatment is recommended at first. It consists of continuous hot or cold fomentations applied locally over the mass, correction of anemia, a high caloric and high vitamin diet and general nursing care. Of the 18 patients in this series of cases, 5 were cured by this regimen. There were 10 patients who did not improve with medical treatment and who were operated on. In three instances a mistaken diagnosis of acute appendicitis was made prior to operation.

At operation an incision which offers an extraperitoneal approach is made over the mass parallel to and above the inguinal ligament. The thick-walled sarcomatoid tumor which is found is incised, and the cavity of the abscess is drained.

Cultures of material from 7 of the 12 patients operated on produced hemolytic staphylococci. It is not understood why inflammation in the retroperitoneal glands produces the hypertrophic tumor so often encountered (fig. 3). Lugones commented on the sarcoma-like appearance of the abscess. Figure 2 shows a section of the wall of the abscess in case 3, which at operation measured 3 cm. in thickness.

When incorrectly diagnosed or neglected, the abscess may point in Scarpa's triangle, at the umbilicus, into the pelvis or into the peritoneal cavity, with fatal results. Rivarola<sup>5</sup> reported a case in which the abscess eroded the iliac artery. With correct diagnosis the prognosis is good. No deaths occurred in the 18 cases of this report. There were 8 deaths among the 92 cases reported in the literature, a mortality rate of 6.7 per cent.

## SUMMARY

Acute iliac adenitis is an uncommon clinical entity, frequently incorrectly diagnosed. It occurs usually in children and is characterized by pain in the iliac fossa, fever and spasm of the psoas muscle. A hard, tender, fixed tumor is palpable above the inguinal ligament. At operation pus is encountered deep in the mass. With adequate drainage recovery is the rule.

The scanty literature on the subject is reviewed, and 18 additional cases are reported.

# NONSPECIFIC MESENTERIC ADENITIS

## A REPORT OF ONE HUNDRED AND FORTY CASES

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There is an ever present fear in the minds of surgeons of failing to recognize acute appendicitis. High mortality and prolonged morbidity are still prevalent as a result of delayed operative intervention. On the other hand, the frequently expressed opinion that it is better to operate in cases in which the diagnosis is incorrect than to overlook a bad appendix has carried physicians far afield. As a result of this state of mind, little thought is given to many diseases presenting symptoms that closely resemble the syndrome of acute appendicitis. The pathologic report on a removed appendix is often no criterion of the actual condition of the abdomen. Such changes as congestion or cellular infiltration are frequently only a comparatively small part of a pathologic process originating elsewhere in the abdomen.

It is of comparatively recent date that mesenteric adenitis has received some attention in medical literature; many of the papers are reports of a few cases in which the diagnosis was not made before operation. Most authors admit their inability to recognize this disease and therefore operate on all patients exhibiting symptoms of appendicitis even when mesenteric adenitis is suspected. Wilensky and Hahn spoke of acute mesenteric adenitis as a distinct disease entity. Their report was outstanding in many respects, but they failed to mention signs or symptoms that would enable the diagnostician to differentiate the disease from acute appendicitis. Pribram, in a lengthy paper, concluded that mesenteric adenitis should be studied more carefully, and he stressed the futility of operation for that condition. In his small series of cases the diagnosis was not made prior to the operation. MacFadden pointed out one possible distinguishing sign, but in my experience it is not pathognomonic and cannot be relied on for a correct diagnosis. Speese gathered a comparatively large number of cases from the literature. He agreed with Wilensky and Hahn that mesenteric adenitis is a disease entity, but he stated that it is impossible to make a diagnosis

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All experiments were performed at the Morrisania City Hospital.

From the surgical departments of the Morrisania City Hospital and the Bronx Hospital.

of the condition. Some authors have stated that the cause is acute appendicitis and that removal of the appendix is necessary.

As will be shown later, the diagnosis of mesenteric adenitis is not an elusive mystery, but is rather simple. It is, however, of the utmost importance to bear in mind the essentials of the anatomy and physiology of the mesentery and of the glands situated between its leaves.

In this series were 140 cases which came to my personal attention. Of the first 100, in every alternate case exploration was made to corroborate the diagnosis.

The mesentery of the small intestine begins at the left side of the second lumbar vertebra near the duodenojejunal attachment and runs diagonally downward and to the right, ending near the right sacroiliac articulation. It is about 15 cm. long at its root, but after spreading out into the shape of a fan it attains a length of 5 meters at its intestinal attachment and is therefore freely movable throughout, except at the ends. The mesentery of the terminal portion of the ileum differs in important details from the rest. A clear understanding of the anatomic arrangement of this area will make the diagnosis simpler. The last 6 cm. of the mesentery of the ileum is free from glands. Its fibers converge from left to right, and no vessels traverse this space. It is often called the avascular space of Treves. On the posterior surface of this fold is a space called the ileocecal fossa; an occasional small blood vessel is seen traversing it from left to right (fig. 1).

The lymphatic drainage of the intestines is accomplished by means of two sets of vessels. One set originates in the mucosa and the submucosa; the other takes its origin in the muscularis and the subserosa. The former is in close association with Meisner's plexus, and the latter with Auerbach's plexus. The submucosal plexuses receive the efferent lymphatics from the intestinal villi draining the lumen of the intestines; those coming from the muscularis and subserosa are fewer and drain the intestinal wall. The efferent lymphatics of the mucosa run directly into the mesenteric leaves, emerging at their attachment to the intestines; those coming from the intestinal wall often run some little distance before joining the more voluminous trunks, with which they enter the mesentery. These combined channels form the collective trunks known as Oselli's chylifers (collectives of the jejunum and ileum). Some authors have described three distinct sets of glands in the mesentery grouped along the avascular arcades. Rouviere, in his extensive studies, failed to find the lymphatic glands in distinct groups. My experiments bear out his observations.

The following experiments were made on living subjects in the course of laparotomies on both animals and human beings. With a 28 gage needle (this size being used to avoid too much pressure), a 1

per cent solution of indigo carmine was injected into the subserosa of the ileum both longitudinally and transversely. The dye ran along the intestinal wall for about 2 cm. and then, turning abruptly downward, entered the mesenteric leaves. The lymphatic channels became clearly outlined in irregular streaks; some of the dye entered glands a little distance from the intestines; the rest proceeded downward. The dye often circumscribed one or more glands, continuing downward toward the spinal column and finally coloring the glands at the root. These were found to be somewhat oval and larger than those at the free border. The drainage from the lowermost part of the ileum (corresponding

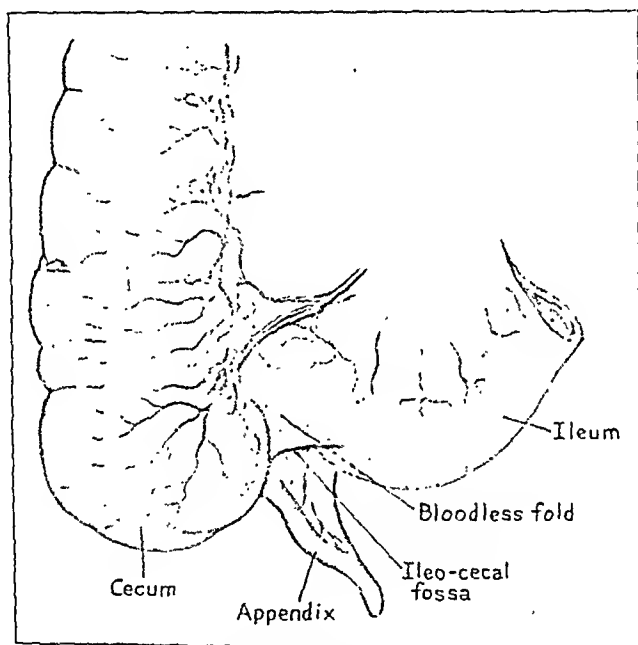


Fig. 1.—The avascular space of Treves, where no glands are found. This area drains into the same chain of lymphatics as do the appendix and the cecum. (After Treves.)

to the avascular space of Treves) is from left to right. The lymphatics run to the satellite nodes of the ileocecal artery. These may join the rare ganglionic nodules close to the iliac branch of the artery or to the terminal branch of the superior mesenteric artery.

The lymphatics of the appendix are not independent of those of the cecum and will be considered together. The cecum has two sets of lymphatics, one set emerging from the anterior wall and another set emerging from the posterior surfaces. Both run toward the ileocecal chain directly or through the intermediary of the anterior and post-

cecal glands. A number of lymphatic glands are found in the ileocecal angle that drain the appendix, the cecum and the lowermost small segment of the ileum. These drain along the mesenteric artery, running diagonally upward and emptying into the chain near the third portion of the duodenum. The glands of the rest of the large intestines are similar to those of the jejunum and the ileum in their arrangement, but are not so numerous (fig. 2).

The physiology of the lymphatics of the small intestines is well known. The retrograde flow described by Braithwaite has not been corroborated. His experiments were carried out on cadavers, and the

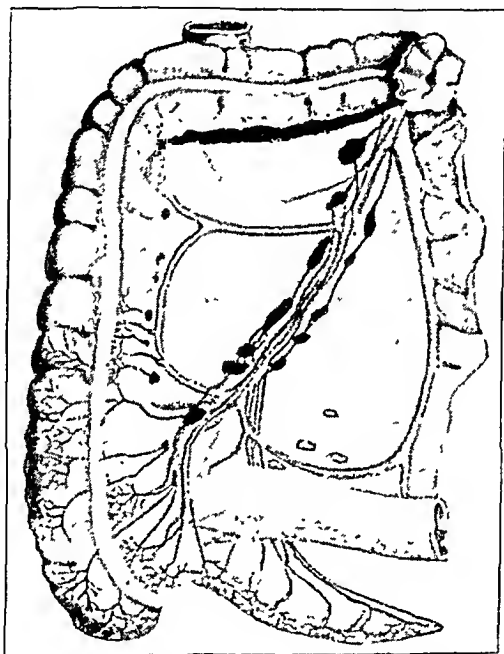


Fig. 2.—Lymphatics of the cecum and appendix. The collected lymph takes the direction of the superior mesenteric artery and empties into the area of the third portion of the duodenum. (Gray, Henry: *Anatomy of the Human Body*, edited by W. H. Lewis, Philadelphia, Lea & Febiger, 1930)

results cannot be substantiated by observations on living subjects. I failed to duplicate his experiments on living animals. The intestinal glands empty into the thoracic duct and thence into the *general circulation*. The reverse process is physiologically not possible.

The pain of mesenteric adenitis is not easily explained, though there is some knowledge of the mesenteric response to external stimuli. While it is true that the intestines are insensitive to such stimuli as cutting, pinching and burning, the ganglionic plexuses of Meisner and Auerbach may be responsive to some forms of stimuli that cannot be

produced artificially. In the mesenteric leaves are found the pacinian corpuscles, which are undoubtedly sensory end organs. The mesenteric leaves are sensitive to pulling in either direction, as can be verified by tying a ligature or by cutting in the course of a laparotomy under local anesthesia. Inflammation and hyperplasia of the glands, causing pressure on the sensory organs, or their direct invasion by toxins is a possible explanation.

The cause of mesenteric adenitis, as was suggested by Wilensky and Hahn, Pribram and others, is absorption of toxins from the intestinal tract. These toxins may be of bacterial origin or may be the products of digestion. The statement that mesenteric adenitis is preceded by an infection of the upper respiratory tract is not borne out by careful histories and close observation. It is also contrary to the normal physiology of the animal body. The fact that mesenteric adenitis is always accompanied or immediately preceded by inflammation of the intestines, as observed at operation, is further evidence that this form of adenitis is a direct result of pathologic conditions in the intestines. There is a small group of cases of very acute involvement in which infection of the upper respiratory tract occurs simultaneously with mesenteric adenitis. In these cases it is perhaps a general toxemia that brings the toxins to the intestines via the blood stream, causing inflammation with consequent glandular hypertrophy. Another possible explanation is that bacteria may pass the stomach, whose normal function is disturbed and its bactericidal action diminished. The organisms entering the alkaline medium of the small intestines proliferate rapidly. In fact, in a great majority of cases, particularly in those of the subacute form, there is no history of a preceding infection of the upper respiratory passages. In only 8 per cent of my series was there such a history.

One often observes that interns rule out mesenteric adenitis as a possibility if no such history of infection is elicited. If the pain is in the right side of the abdomen it is usually diagnosed as subacute or chronic appendicitis. Another observation is that mesenteric adenitis occurs mostly in the small intestines, and in the majority of cases in the lower 4 or 5 feet (124 to 152 cm.) of the ileum (except in the avascular space of Treves). Here the intestinal products of digestion are toxic and absorption is great. The statement, frequently heard, that this form of adenitis is due to an inflamed appendix is utterly incorrect and contrary to anatomic arrangements. As pointed out by Wilensky and Hahn, in acute appendicitis the mesenteric glands of the ileum are not involved. In this connection it may be pointed out that postoperative abdominal pain, so often felt by young adults, occurs mostly after so-called subacute or interval appendectomies. It is usually explained by the timeworn aphorism of postoperative adhesions or neurosis. Pribram's statement that such pain is in many cases due to

continued inflammation or to repeated attacks of mesenteric adenitis is probably correct. Felsen suggested that the cause factor of mesenteric adenitis may be a form of bacillary dysentery. In this series no thorough study was made, but of 30 studied cases in only 3 was there positive agglutination. The general impression that diarrhea accompanies enteritis is erroneous, as was pointed out by Felsen in his studies of bacillary dysentery.

When the abdomen is explored a few days after the onset of the disease, the acute inflammation of the intestines may have subsided. There remains, however, some thickening of the wall, and the color is often seen to be a light pink. Perhaps in some cases the toxins enter the lymphatic channel directly from the mucosa without affecting the wall of the intestines.

The frequency of mesenteric adenitis cannot be estimated with any approach to accuracy. For 18 of 100 consecutive children and adolescent patients admitted to my service in the wards with a diagnosis of acute or subacute appendicitis, a diagnosis of mesenteric adenitis was made after examination and proved correct at operation. Still, quoted by MacFadden, found that 59 per cent of children on whom autopsy was performed had enlarged mesenteric glands. This disease is prevalent in children and adolescents and is rare in adults. I have observed only 1 adult patient, a man 30 years of age. I failed to make a diagnosis, his being one of the early cases. The youngest patient in whom the disease was recognized was 3 years old. The average age of the patients in this series was 12.1 years; 58 per cent were girls and 42 per cent boys.

That the diagnosis of mesenteric adenitis is not difficult may be gathered from the fact that my house surgeons have learned to recognize this condition with remarkable frequency. In this series we had 2 cases in which the condition was not diagnosed correctly, the case of the 30 year old man, just mentioned, and the case of a child acutely ill, with a temperature of 105 F., in which we made the diagnosis of toxemia due to streptococcic infection of the throat, with inflammation of the intestines and the mesenteric glands. A note on the chart mentioned the possibility of appendicitis but added that the patient was too ill to be operated on. After thirty hours, when the temperature was much lower an exploratory laparotomy was performed and acute appendicitis was found. The whole intestinal tract was highly inflamed, the intestinal wall much thickened and the glands in the mesentery enlarged. The patient recovered.

Nonspecific mesenteric adenitis can be roughly separated into three types. The first is the least common and in this series only 8 cases occurred, all the patients being between 6 and 12 years of age. A sudden onset within twenty-four hours, with a temperature ranging

between 105 and 106 F. and marked toxemia, were common to all. The blood picture in such cases is apt to be alarming. A white cell count amounting to 20,000 or more, with a differential count showing from 80 to 90 per cent polymorphonuclears, is common in the first twenty-four or forty-eight hours. The proportion of band forms may be as high as 30 per cent. All these symptoms occur within the first six hours of the onset. Examination of the patient reveals the following picture: a flushed face, rapid pulse and marked congestion of the throat. If the patient has been ill more than twenty-four hours a membrane covering the tonsils may be seen. The abdomen is somewhat distended and tender throughout, especially in the right lower quadrant. When operated on the whole intestinal tract, particularly the small intestines, is thickened and extremely red. In the mesentery the glands are found to be deep pink. Those near the intestinal attachment are small, round and of deeper color, while those near the root are larger and somewhat oval. The appendix is congested, as is the cecum.

With the second type, which is the most common and is often mistaken for appendicitis, there usually is the following history: The patient is a child or a young adolescent and complains of intermittent abdominal pain which has lasted for one day or longer. The pain is at first rather severe but becomes somewhat less so on the second day. Nausea is present, but vomiting occurs only in about 40 per cent of the cases. When vomiting is present it usually occurs four hours or more after the onset. The pain may subside for a few hours but recurs at frequent intervals. When questioned as to the location of the pain the patient will point to the right lower quadrant of the abdomen. There is neither constipation nor diarrhea. In the first twenty-four hours the temperature ranges around 102 or 103 F., but it recedes within twelve to twenty-four hours to approximately 100 or 101 F. The blood count during the first day is about as follows: the number of erythrocytes is normal; the number of white cells is high, often 18,000, with a differential count showing 80 per cent or more polymorphonuclear leukocytes. The shift to the left is between 12 and 20 per cent. The following day the white blood cell count recedes to about 10,000 and the shift to the left recedes in a similar proportion. Results of urinalysis are negative.

In a recumbent position the patient appears comfortable. Abdominal reflexes are normal, since the parietal peritoneum is not involved. Gentle percussion may elicit slight tenderness about 4 cm. to the right and a little below the umbilicus. This is the first differential point, as in appendicitis gentle percussion will always elicit pain over the base of the inflamed appendix. On palpation, no rigidity can be discovered, though at times there is a mild resistance over the right side which can be easily overcome when the patient's attention is diverted. There is always a moderate degree of rebound tenderness throughout the lower



part of the abdomen, but the sudden removal of the palpating hand from the left lower quadrant does not cause rebound tenderness on the right side. Tenderness is found over a small area to the right of

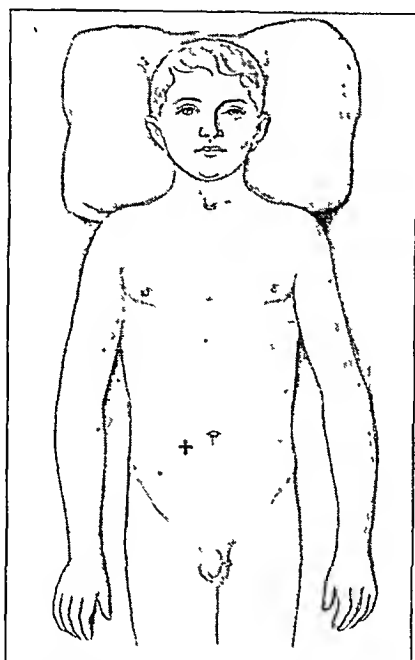


Fig. 3.—The tender point in mesenteric adenitis is at a higher level than in appendicitis and is internal to McBurney's area.

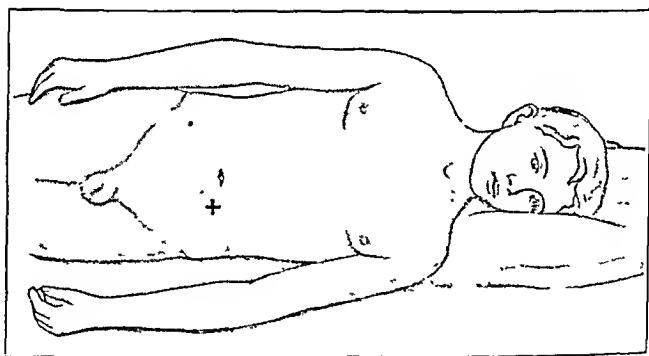


Fig. 4.—When the patient is turned to and allowed to rest on the left side, the tender area is shifted to the left and is absent on the right, as indicated by the cross.

the umbilicus, but much higher than McBurney's point. The tender area may extend even above the umbilicus on the right side. The left side at this time is free from tenderness. The patient is then turned on the left side and allowed to remain in this position for thirty seconds

or more. Palpation in this position finds the tender area previously noted on the right side now shifted to the left of the umbilicus and absent on the right side (figs. 3 and 4). The patient is turned on the right side and allowed to rest for a short period, and palpation then reveals absence of tenderness on the left side and more marked tenderness on the right. In this position the tenderness in the area in question is more extensive than when the patient was resting on his back. This shifting tenderness is easily explained if one remembers the anatomic outline of the mesentery. When the patient is turned on either side the mesentery and small intestines will gravitate to the extreme dependent part of the abdomen. The cecum and appendix have little mobility and cannot be shifted to the left with a change of

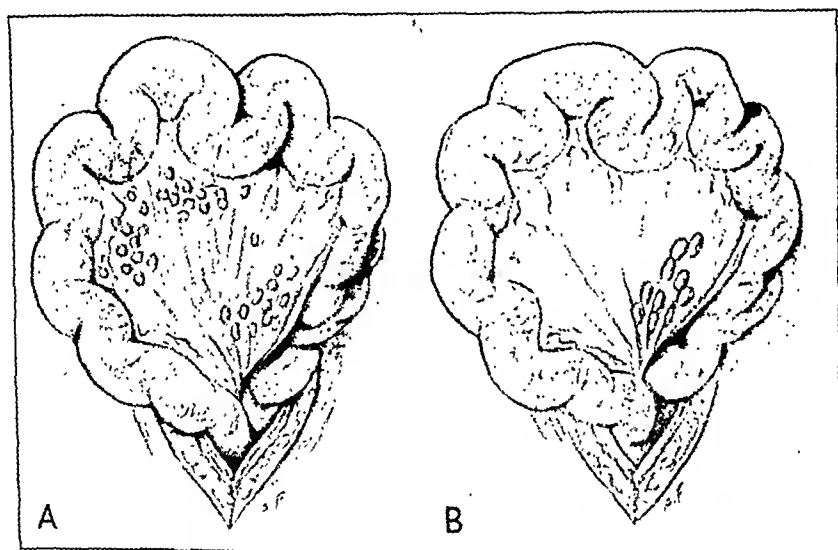


Fig. 5.—*A*, early stages of hyperplasia. The glands are found near the intestinal attachment of the mesentery and at the root. *B*, appearance three or more days after the onset. The glands are absent near the intestinal attachment of the mesentery but persist near the root.

the position of the body. This one sign, when present, has always differentiated mesenteric adenitis from acute appendicitis. The findings at operation in this type of mesenteric adenitis depend on the length of time which has elapsed since the onset. If exploration is made during the first twenty-four hours, the findings are somewhat as follows: The small intestine shows inflammation, which is most marked in the last few feet of the ileum. This inflammation may be segmental, that is, one may find areas of inflammation with intervening parts of normal appearance. The glands are usually small and pinkish near the mesenteric attachment, while lower down they are larger and oval (fig. 5 *A*). If operation takes place three or more days after the

onset, the small intestine may be found normal in appearance, but thickened, and the mesentery near the intestines free from glandular enlargements. Lower, nearing the spine, the glands are present in small groups and are lighter in color (fig. 5 *B*). They sometimes attain the size of a small walnut. In cases of recurrent involvement the glands are found near the spinal attachment and are never so large. These are much harder than in the early stages. This condition may persist for a long time. In some cases when operation is delayed one or more weeks the ileum is found normal in appearance. It is perhaps possible



Fig. 6.—Various stages of mesenteric hyperplasia in nonpyogenic adenitis of the mesentery.

that absorption of the toxic agent takes place directly into the mesentery lymphatics from the mucosa without involving the muscularis and the serosa.

The third type gives the same history as the second, but with this type examination of the abdomen discloses that whereas the tenderness can be shifted from right to left with change of position there persists a tenderness over the cecum. This type cannot always be differentiated from a pathologic process which involves the appendix. The findings at operation are somewhat as follows: The small intestine, particularly the lower ileum, is moderately inflamed, the cecum more so.

In the mesentery of the ileum the glands are enlarged. In the ileocecal angle is found a conglomeration of four or five glands markedly infiltrated, and the appendix is congested and much thickened. In this connection it is interesting to note that one often hears cases of the condition just described reported as proving that mesenteric adenitis is caused by an acute condition of the appendix. The explanation of this pathologic process lies, in my opinion, in the occurrence of an intestinal infection, due either to putrefaction or to bacterial invasion, which causes an inflammation of the ileum, the cecum and part of the ascending



Fig. 7.—Various stages of mesenteric hyperplasia in nonpyogenic adenitis of the mesentery.

colon. The involvement of the appendix in these cases is only part of the whole process. A contributing factor is possibly interference with the normal circulation of blood in the appendix by the enlargement of the glands in the ileocecal angle. The patients must be watched carefully. If rigidity occurs and the polymorphonuclear leukocyte count remains high, the abdomen must be explored. This form of ileitis should not be confused with the terminal ileitis described by Ginzberg and Crohn and others. The pathologic process and the symptoms of terminal ileitis are entirely different, and the course is progressive. In this series I have not encountered the pyogenic form of adenitis.

The pathologic report of the appendixes and glands removed during laparotomies in these cases is of special interest. From all patients laparotomized the appendix was removed, and in 20 cases one or more glands were removed for study. Felsen studied some of these appendixes by injecting the lumen with barium sulfate and correlating his findings with the histologic evidences, using a suitable number of normal controls. He found the mucosa intact, and sections failed to show actual pathologic conditions. Congestion was present in a small number of the appendixes. All glands removed proved to be sterile on culture; sections showed cellular infiltration, as can be seen in figs. 5 A, 6 and 7.

For the patients on whom operation had not been performed and who were under observation in the hospital for five days or more, the following routine was adopted: All solid food was interdicted for at least four days. During this period fruit juices were given freely and boiled milk in small quantities. Liquid petrolatum was given to overcome possible constipation, but all irritating cathartics were avoided.

The patients operated on had an uneventful convalescence.

As most of the patients were in the wards a thorough follow-up was impossible. Only 50 patients (25 of whom had been operated on) were observed from one to two years after either observation or operation. Both sets of patients had repeated mild attacks of abdominal pain. An interesting observation was that private patients not institutionalized continued to have severer attacks of pain than those kept under observation in the hospitals, though the latter came from much poorer surroundings.

#### CONCLUSIONS

1. Mesenteric adenitis is much more common than is generally recognized.
2. A diagnosis is possible in a majority of cases.
3. Mesenteric adenitis is not necessarily an accompaniment of an infection of the upper respiratory tract.

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# DISTRIBUTION AND EXCRETION OF WATER AND CHLORIDES AFTER MASSIVE SALINE INFUSIONS

AN EXPERIMENTAL STUDY

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Massive intravenous infusion has become an accepted therapeutic measure of wide application among practitioners of medicine and surgery, and present trends in medical practice seem to indicate even more extensive use of the method in the future. Nevertheless, comparatively little is definitely known about the physiologic responses of the body to the direct artificial addition of solutions of inorganic substances to the circulation. This is because the procedure has developed primarily at the bedside rather than in the experimental laboratory. Moreover, as ordinarily practiced, it has proved almost completely devoid of danger to life.

Because of the simplicity of the common vehicles of infusion—watery solutions of sodium chloride and dextrose usually—the consideration of intermediate metabolism has not seemed to most practitioners a serious issue, and the attention of experimentalists has turned, rather, to such matters as the causation and prophylaxis of the postinfusion reaction. It is true that attention has been paid to the assimilation and elimination of dextrose when used in infusions, and some consideration has been given to the factor of hypertonicity. By and large, however, the fundamental proposition that parenterally administered fluids are the physiologic equivalents of the same fluids administered by mouth has never been subjected to thorough experimental investigation.

The experiments to be reported in this communication were originally designed to determine the maximum rate of infusion compatible with survival and the lethal dose of essentially isotonic solutions of sodium chloride. It was moreover proposed to discover the cause of death after such lethal infusions and to trace the intermediate assimilation, trans-

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location and excretion of both the sodium chloride and the water when given in just sublethal amounts. As so frequently happens in experimental work, the original aims have not been entirely fulfilled, but important facts have, we believe, been collected. This investigation is, of course, but part of a much larger one, involving parenteral administration of solutions in other concentrations, of other substances and by other methods than intravenous injection. Until the general problem has been studied in all of these aspects, it cannot be assumed that the results of this study are applicable to all types of parenteral administration.

#### TECHNIC

In the experiments now to be reported, cats exclusively were used as experimental animals. No particular selection of animals was made with respect either to size or to physical condition. They were stock animals, which for varying periods had been fed ordinary laboratory rations, including as much water as they would drink.

Intraperitoneal injection of solution of dial and ethyl carbamate (urethane)<sup>1</sup> (0.9 grains [0.054 Gm.] of diallylmalonylurea per kilogram of body weight) was practiced routinely for anesthesia. In a few instances, in which the initial level of anesthesia produced by this agent was not deemed sufficiently deep, a little ether was temporarily given by inhalation to facilitate the primary operative procedures.

The intravenous infusions were given from a standard graduated arsphenamine buret holding 300 cc., which was connected by means of a short piece of rubber tubing to a glass cannula. This was inserted into the jugular vein (usually on the right) except in some cases in which the femoral vein was selected for special reasons. The arsphenamine tube was attached to a buret stand at such a level that the height of the column of fluid above the cannula varied from about 25 inches (63 cm.), when the tube was full, to about 16 inches (40 cm.), when the level of fluid had dropped to the last graduation.

In such a gravity system the speed of injection depends not only on the head of hydrostatic pressure but on the available caliber of the injectional system at its narrowest point, which ordinarily is the point of junction between the venous cannula and the vein. This narrowest part of the system is subject to variations in caliber from moment to moment because of such factors as twisting or change in angulation of the cannula with respect to the vein. These variations cannot be altogether avoided because living animals cannot be absolutely immobilized. Because we were anxious to maintain strictly constant rates of injection, we originally used the principle of the Mariotte flask in order to stabilize the hydrostatic pressure. We soon found, however, that the variability which resulted from fluctuations in the pressure was of little importance compared with that due to changes in caliber. Therefore, we ultimately fell back on the simple expedient of keeping the system adjusted practically to the full caliber of the vein. Minor variations were compensated by slight manipulation of a screw clamp and all our adjustments gaged by constant checking of the rate of fall of the meniscus in the buret.

We sought to avoid as much as possible the debatable point as to how strong a solution of sodium chloride constitutes an exactly isotonic or physiologic solution

1. Obtained through the courtesy of the Ciba Company.

for the cat. Therefore, we have arbitrarily selected the strength of 1 per cent as being sufficiently close to the proper value for practical purposes. This figure is nevertheless not so exactly the proper value as to make it appear that we consider isotonicity actually critical.

In most of the acute experiments tracheal cannulation was performed, and blood pressure and respiration were continuously recorded on a long paper kymograph. The blood pressure was taken by direct cannulation of the common carotid artery and the respiration recorded from the tracheal cannula through a rubber tube connecting with a sensitive tambour.

#### PRELIMINARY EXPERIMENTS TO DETERMINE THE "LETHAL DOSE" OF SOLUTIONS OF SODIUM CHLORIDE

Our recorded tabulation (table 1) includes results from 10 cats. A considerably larger number of animals was actually used, omissions in

TABLE 1.—*Rates of Injection and Total Amounts of Sodium Chloride and Water in Lethal Doses of Saline Solutions Administered Intravenously\**

Cat Number	Strength of Sodium Chloride Solution, %	Weight of Animal in Kg	Rate of Injection in Cc. per Kg. of Body Weight per Min.	Total Volume in Cc. per Kg. of Body Weight	Total Sodium Chloride in Cc. per Kg. of Body Weight per Min.
2A	1	1.53	7.71	503	5.03
9A	1	2.95	6.68	517	5.17
10A	1	2.77	4.04	639	6.39
11A	1	2.88	4.44	446	4.46
3A	2	2.50	5.68	320	6.41
4A	2	2.78	4.53	241	4.82
7A	2	2.90	5.93	196	3.93
8A	2	3.45	3.24	362	7.24
6A	5	2.40	1.66	170	8.50
5A	10	1.76	4.23	55	5.51

\* The injections were continued at a constant rate until death occurred.

the final record being made in order to avoid unnecessary compounding of evidence. Four cats received a 1 per cent solution of sodium chloride, 4 others a 2 per cent solution and the 2 remaining a 5 per cent and a 10 per cent solution, respectively.

The death of the animals in all cases was obviously due to the injection of sodium chloride in water, and the fatal dose is a matter of record. It is not, however, strictly accurate to speak of this as the lethal dose in the same sense as that in which the term is applied to intrinsically toxic substances. Both water and sodium chloride are, of course, normal constituents of the blood stream, and they become toxic only fortuitously, when their relative concentrations are grossly disturbed. The data for the first and the last animal of the preceding table clearly exemplify this statement, since both received approximately the same amount of sodium chloride, yet the first tolerated approximately nine times as much water as the last before death occurred, the solution which the last received being ten times as concentrated. Intermediately placed in the

series are 2 animals, 9A and 10A, which received considerably greater amounts of water than either of the other 2 animals. From these observations it may be concluded that water is not the lethal agent.

Furthermore, sodium chloride does not appear to be the lethal agent either, for there are animals intermediate in the series, 3A, 6A, 8A and 10A, which tolerated before death occurred considerably greater amounts of sodium chloride than did either the first or the last animal.

The logical conclusion is, of course, that neither of these agents is toxic in itself and that separately, therefore, they cannot be said to have any assignable lethal dose. In combination, however, they do appear to produce death after certain amounts have been given. The necessary amount depends on the concentration of the salt in the solution and undoubtedly also on the rate of its administration. The lethal dose of any given solution injected at any given constant speed is undoubtedly constant for any given concentration.

That hypertonicity (or hypotonicity) is a factor of great importance in determining the lethal dose is strongly indicated by the reactions of the animals in this short series. They appeared definitely less tolerant of a 2 per cent solution than of a 1 per cent solution. In still higher ranges of concentration (5 per cent and 10 per cent) it appears that much smaller amounts are fatal. At such concentrations rates of injection must be greatly reduced or death ensues rapidly.

The only conclusion for our present purposes which we wish to draw from this short series of animals is that cats tolerate the intravenous injection of tremendously large amounts of solution of sodium chloride at a rapid rate, provided the solution is not more concentrated than 2 per cent. The lethal amount is of the order of 500 cc. per kilogram of body weight for 1 per cent solutions and 275 cc. for 2 per cent solutions when the injection is made at the speed of approximately 5 cc. per kilogram of body weight per minute. Translated into terms of a human being weighing 70 Kg., or 154 pounds, this would be a total of 35 liters of 1 per cent solution, given at the rate of 350 cc. per minute. This is, of course, a much more massive volume and a much more rapid rate of injection than is actually used in clinical practice. It is therefore questionable whether death has ever resulted in a human being merely from the injection of the weaker solutions of sodium chloride, as such.

Milbert<sup>2</sup> said that he felt he had grossly exceeded what are customarily considered the limits of safety when he used in a series of clinical cases a rate of injection between 0.83 cc. and 2.5 cc. per kilogram of body weight per minute, though the total amount of solution was

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2. Milbert, A. H.: Infusion Reactions with Special Reference to "Speed Shock," *Am. J. Surg.* **26**:479-485, 1934.

in many cases less than 1,000 cc. To be sure, he used some solutions which were hypertonic (2 per cent and 5 per cent solutions of sodium chloride and 10 per cent solutions of dextrose). The fact that Milbert's patients suffered no ill effects attributable to the rate of infusion corroborates the belief that such quantities and rates are conservative rather than radical.

It is not a new or recent observation that experimental animals tolerate the intravenous infusion of huge quantities of saline solution. Dastre and Loye<sup>3</sup> published in 1888 a convincing communication describing the introduction of suitable fluids (0.7 per cent solutions of sodium chloride) into the circulation of rabbits and dogs. They injected amounts totaling as much as three quarters of the body weight within the relatively short period of three to seven hours. These injections produced no unfavorable effects, either immediate or remote, in two months of observation. We can corroborate this result unreservedly for postinfusion periods of several days to two weeks, though we have seen no occasion to prolong the observation of recovery beyond such limits.

A. EFFECT OF MASSIVE INFUSIONS ON BLOOD PRESSURE.—The capacity of the vascular system is constantly shifting by virtue both of (1) its vasomotor reactions, which tend to adapt its capacity to the cubic measure of its contents, and of (2) the permeability of its immense capillary system, which seems to change both locally and generally in accordance with a number of different physical and chemical factors. It is therefore impossible by any means at present available to determine how long any artificially injected soluble substance remains in the circulation. This is particularly true of solutions of sodium chloride because of their extreme diffusibility.

The best that can be done is to attack the problem indirectly. A long series of tracings of blood pressure, taken during the large, rapidly administered infusions which we have employed, serves to show conclusively that the blood pressure is neither constantly nor greatly affected. A representative tracing, somewhat condensed, is reproduced in figure 1.

In general, if the blood pressure is somewhat low at the time the infusion is started a temporary rise is produced, which tends to be well sustained. If, on the contrary, the blood pressure is moderately high at the beginning of the infusion, it customarily decreases slightly within a short time and thereafter remains at about the same level throughout the infusion. In general, the blood pressure is maintained at a satisfactory level throughout a fatally large infusion and falls abruptly just

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3. Dastre, A., and Loye, P.: *Le lavage du sang*. Arch. de physiol. norm. et path. 2:93-114, 1888.

as death is occurring. A slight progressive decrease in blood pressure throughout the entire course of the infusion is the rule.

Every indication points to a marked increase in the volume of circulating blood during such infusions. Hematocrit estimations show increasing preponderance of fluid over cells and increase in the water content of the blood is revealed by drying successive samples to constant weight. Therefore a fairly stationary blood pressure at a relatively high level can mean only that great compensatory vasodilatation occurs.

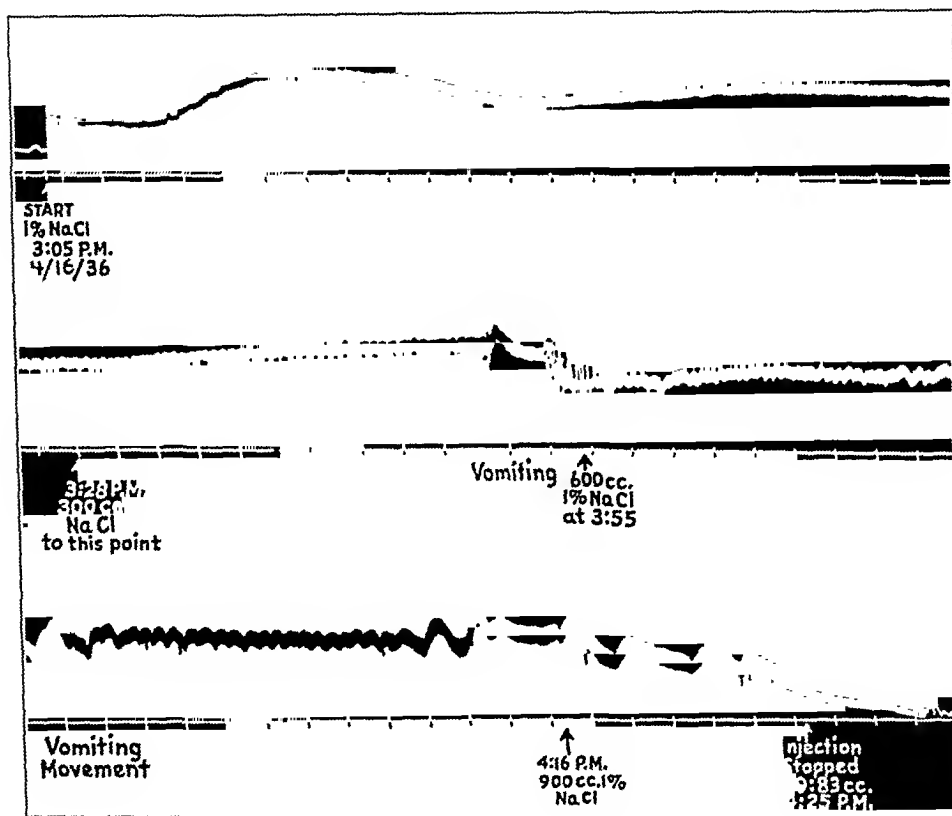


Fig. 1.—A characteristic tracing of blood pressure; the kymogram has been cut in three sections, which are reproduced one under the other. Note the relatively constant level sustained throughout a continuous massive infusion of 1 per cent solution of sodium chloride (983 cc. in a cat weighing 1.76 Kg.).

B. GROSS PATHOLOGIC OBSERVATIONS.—It was hoped that examination of the various tissues and organs of the cats at autopsy would give some definite clue as to the cause of death after massive infusions. This hope was by no means completely fulfilled, for although definite changes were evident they were diffuse, and it was therefore impossible to attribute the fatality to the failure of any particular organ or system.

For the animals which died from the effects of massive doses of 1 per cent saline solution typical postmortem observations were as follows:

*General Appearance.*—The animal's abdomen was considerably distended; watery yellow fecal material was streaming from the rectum; urine was trickling from the urethra, and watery mucoid material was dripping from mouth and nose.

*Peritoneal Cavity.*—The peritoneal cavity contained some slightly blood-stained free watery fluid, the amount of which was estimated at 100 cc. (The staining with blood was probably the result of the action of dial on the peritoneum.)

*Gastrointestinal Tract.*—The walls of the stomach were thick, white and edematous; the cavity of the organ contained a small amount of bile-stained watery material. Both large and small intestine were thick, white and edematous; both were moderately filled with watery fecal material. The amount of material which the gastrointestinal tract contained was much less than one would suppose from the appearance of its various parts before incision. Most of the apparent distention which was seen from the peritoneal surface was actually due to the great thickness of the walls of the intestine.

*Pancreas.*—The pancreas was completely water logged, pale pink and friable; the structural elements of the organ were widely separated by gelatinous material. Altogether, the organ was several times its normal size. The cut surface did not exude much fluid unless squeezed or minced with a knife.

*Kidney.*—The organ showed no particular enlargement. The capsule stripped easily. Thus exposed, the organ was pale and tense and bled freely from its cut surface.

*Adrenal Glands.*—Except for some possible enlargement, the adrenal glands were apparently normal.

*Urinary Bladder.*—The bladder appeared distended, but when it was opened the appearance seemed to be due not so much to the quantity of urine it contained as to the thick, edematous condition of its walls. Such urine as it did contain was clear and colorless.

*Gallbladder.*—The gallbladder was dark bluish green and was distended with bile.

*Liver.*—Aside from some questionable enlargement, the liver presented a normal appearance.

*Retroperitoneal Space and Space Between the Leaves of the Mesentery.*—These spaces presented a remarkable appearance, as if widely distended with fluid. Cutting into the tissues, however, revealed that the appearance was due to a gelatinous edema rather than to an accumulation of free watery material. Little fluid escaped spontaneously from the cut surface.

*Thoracic Cavity.*—There was judged to be a slight excess of free fluid in the thoracic cavity. It was clear and watery in appearance, and its amount was estimated at 10 cc.

*Lungs.*—The dependent portions of both lungs were dark red and mottled; the upper lobes were pink and crepitant. The entire organ showed a frothy edema when cut and squeezed, and the lower lobes exuded a clear, serous fluid from the cut surface, which dripped when this part of the organ was compressed. Squeezing the entire organ caused frothy exudate to appear at the opening in the neck formed by tracheotomy.

*Salivary Glands.*—The salivary glands were swollen, pale and edematous.

*Other Tissues and Organs.*—All other organs, including the thyroid gland, the brain and the heart, appeared normal. In general, the tissues were diffusely pale, swollen and edematous, but they did not pit on pressure.

The observations on the animals which died from the infusion of 2 per cent solution of sodium chloride were superficially similar, but different in certain details. The elements of similarity included the abnormal amounts of free fluid in the abdominal cavity, the characteristic and striking gelatinous edema between the leaves of the mesentery and in the retroperitoneal space, the gelatinous edema of the pancreas and the watery edema of the stomach, intestine, and salivary glands. Among the most characteristic respects in which the latter group of animals differed from the former were the following:

1. Although the intestine was white and edematous, the small intestine was tightly contracted and beaded, the large intestine only being dilated.
2. The kidneys, though somewhat swollen, instead of being pale were dark and brownish, and the cut surface showed hemorrhagic areas about the pyramids.
3. The heart showed extreme contraction, with complete emptying of all its chambers.
4. The lungs showed much less edema, but scattered areas of punctate hemorrhage were noted.

*Comment.*—All in all, comparison of the postmortem observations on the animals which died from the effects of the 1 per cent solution and those on the animals which died from the effects of the 2 per cent solution tends to support the view that the physiologic mechanisms which produced death in the two groups were probably not the same. If the animals which died from the effects of less concentrated solutions succumbed to the bulk of the fluid injected, the animals which died from the effects of more concentrated solution probably succumbed to osmotic derangements.

Survival experiments in which just sublethal amounts of 1 per cent solutions of sodium chloride were administered apparently demonstrate that the pathologic changes just described are all reversible up to a sharp end point beyond which death inevitably occurs. If the infusion is stopped at any stage prior to the actual onset of death, the animal invariably recovers completely. If representative animals are killed at various intervals during the period of recovery, which lasts twenty-four hours or slightly longer, the changes in the various tissues and organs are seen to be progressively disappearing. At the end of about twenty-four hours all tissues and organs appear normal again, and no vestige of the former gross changes is to be observed.



At the risk of anticipating confirmatory physical and chemical evidence, it is suggested that after the massive infusion of essentially isotonic saline solutions death is due to no single factor. In such cases the cause of death is therefore not to be found in changes in any particular organ or system. Death probably results, rather, from a generalized physiochemical imbalance, the exact nature of which it is at present impossible to determine. It seems likely that normally reversible changes of a diffuse nature are gradually pushed further and further when the rate of infusion greatly exceeds the rate of excretion. Ultimately the organism is more or less suddenly overwhelmed, and death comes as a widespread physiochemical collapse.

This was the opinion of Dastre and Loye,<sup>3</sup> who concluded that tolerance to large intravenous infusions depended primarily on the rate of injection. If it did not exceed the combined capacities of the emunctories and the mechanisms for storage, part of the injected fluid was excreted, and the rest remained in the tissues. In such a case, they declared, accommodation was complete, and the net result was nothing more than a washing of the blood, a *lavage du sang*. When, on the contrary, the rate of injection was excessive, the emunctories could no longer increase their rate of elimination to such an extent as to keep pace with it. When this occurred, accumulation in the tissues soon exceeded the capacity for physiologic storage, and ultimately mechanical effects due to the inflow of the fluid overwhelmed the animal.

Before the discussion proceeds to other matters, the subject of accidental or adventitious death should receive some special consideration. Unless certain precautions are observed and sometimes in spite of the observance of these precautions, animals may succumb as the result of much smaller intravenous infusions of entirely compatible fluids. This is likely to occur particularly when solutions are hypertonic and when rates of injection are rapid.

The most frequent cause of these accidental or adventitious deaths is vomiting or regurgitation under conditions in which the swallowing reflex is abolished or obtunded. Under such conditions the regurgitated material may never appear at the mouth to give a hint of what is actually happening, and the usual convulsive muscular movements of the vomiting act may be in abeyance. Death occurs, nevertheless, because of aspiration of the regurgitated material into the respiratory tract, and the animal drowns in its own secretion. Doubtless the activity of the bronchial, pulmonary and salivary secretory mechanisms under the stimulation of intravenous infusion acts as a predisposing cause of this suffocation. Perhaps also the acidity of the gastric secretion which is inspired as a result of regurgitation is important as a precipitating cause. At all events, autopsy of an animal which has died for no apparent cause

during intravenous infusion almost invariably reveals the trachea and both bronchi full of frothy mucous and gastric secretion. Rarely frothy exudate appears at the nose and mouth before death; it can almost invariably be expressed mechanically after death by squeezing the exposed lungs. Two facts sufficiently confirm this statement of the cause of death: 1. If preliminary tracheal cannulation is performed death does not occur, in spite of the fact that such a procedure presumably does not interfere with the tracheal, bronchial and pulmonary secretory mechanisms. In short, death does not occur as a result of pulmonary edema as such. 2. If records of blood pressure and respiration are traced in animals not subjected to preliminary tracheal cannulation, they always show that such deaths are shortly preceded by the increased respiratory excursions and the profound depression of blood pressure which are characteristic of occult vomiting.

We are convinced that this is the explanation of some of those sudden deaths which occur during infusions. Such deaths previously have been assigned to other causes; thus Hirshfeld, Hyman and Wanger<sup>4</sup> described under the title of "speed shock" a condition which seems to fall within this category. They stated, as a result of a series of experiments, that the condition of speed shock could be produced by introducing intravenously as little as 1 or 2 cc. of solution, provided the solutions were introduced by hypodermic syringe and needle "as rapidly as the plunger could be pressed." The reaction which they described occurred within from forty to sixty seconds and included salivation, vomiting, diarrhea, dyspnea, muscular atony or at times muscular spasm and incoagulability of the blood. It was preceded by or associated with abrupt depression of the blood pressure. "At one time or another . . . in whole or in part" they were able to produce the condition with a wide variety of substances in solution as well as with insoluble substances, though "inconsistency and inconstancy" of symptoms were the rule.

In spite of many trials we have never been able to produce this phenomenon by using essentially isotonic solutions of sodium chloride, even in 10 cc. amounts and violently forceful injections. Hypertonic solutions, however, especially after animals have already received considerable amounts of fluid, are very likely to produce the vomiting reaction which we are convinced is the basis of the phenomenon. Presumably many of the substances used by Hirshfeld and his co-workers are particularly likely to stimulate the vomiting reflex.

Incidentally, it may be of interest to note that workers like Dastre and Loye<sup>2</sup> who have extensively employed rabbits in their experimental

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4. Hirshfeld, S.; Hyman, H. T., and Wanger, J. J.: Influence of Velocity on the Response to Intravenous Injections, *Arch. Int. Med.* 47:259-287 (Feb.) 1931.

work are not likely to have noted the phenomenon, for rabbits have a poorly developed vomiting mechanism. Experimenters who perform preliminary tracheotomy do not see death from this cause for the obvious reason that tracheotomized animals cannot inspire what they regurgitate. Furthermore, if the vomiting mechanism is not productive of actual regurgitation death does not ensue, and the only result is transitory hyperpnea and depression of the blood pressure, which would correspond to nonfatal "speed shock" (fig. 2).

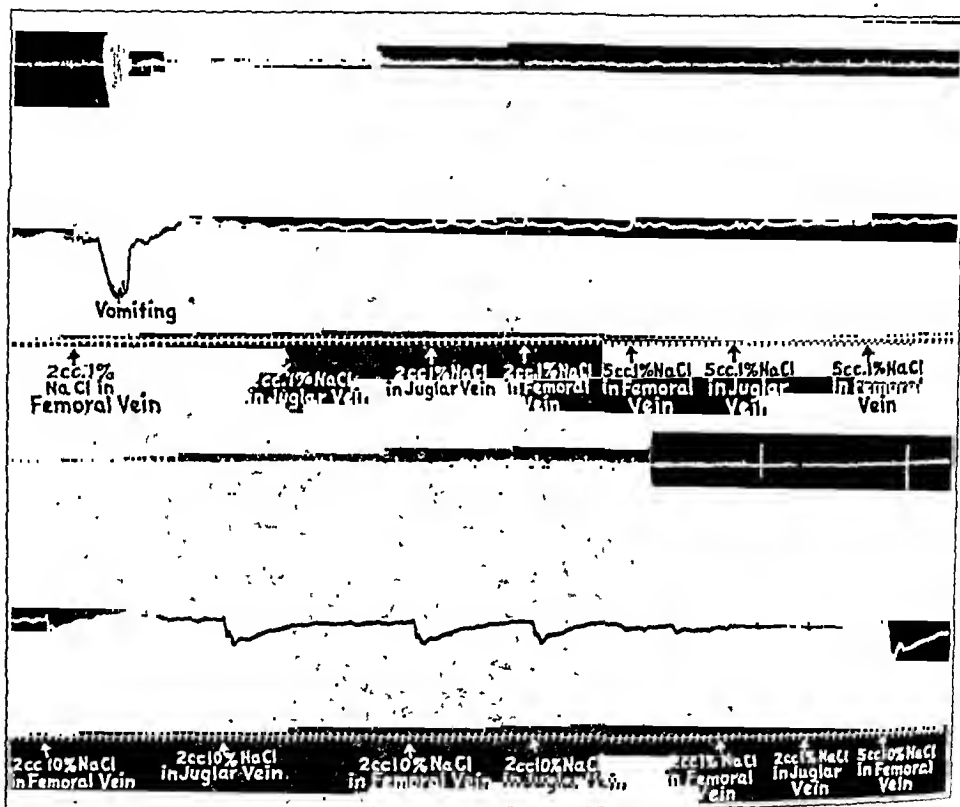


Fig. 2.—A series of attempts to produce "speed shock" by forcefully introducing small amounts of saline solution into the circulation. The very first injection (2 cc. of 1 per cent solution of sodium chloride) was followed by vomiting—extreme upper left corner. This was accidental, as indicated by the fact that repetitions of the same dose, injections of larger amounts of the same solution, and injection of small amounts of various hypertonic solutions failed to elicit the phenomenon a second time. Very hypertonic solutions (see lower panel) do produce variable momentary reductions in the blood pressure.

It is important also to avoid "pyrogenic" products in the distilled water employed in the compounding of solutions for injections and contamination of the paraphernalia used in such injections by "pyrogenic substances." The role of these substances in the production of post-

infusion reactions has been investigated by Rademaker,<sup>5</sup> following the lead of Seibert.<sup>6</sup> Although the only precaution against the inclusion of pyrogenic substances in our solutions has been fresh single distillation of water through an ordinary laboratory still and immediate sterilization by boiling, we have only occasionally encountered effects attributable to such a factor. On several occasions, however, we have attempted the use of solutions which had previously stood in the laboratory for several days under conditions which were compatible with the development of pyrogenic substances and have encountered deaths attributable to no other cause that we could determine. The use of a freshly and accurately compounded solution has obviated all difficulty from this source. On this basis we are convinced, though admittedly on insufficient evidence, that the possible presence of pyrogenic substances in infusions given to laboratory animals cannot be overlooked with impunity.

#### TRANSLOCATION OF WATER AND CHLORIDES

A moment's preliminary consideration of the wide fluctuations in the intake of water to which the body is accustomed should lead one to expect a well developed and probably complex mechanism for its translocation after absorption.

It should be emphasized that ordinarily water is not rejected by the gastrointestinal tract, regardless of the quantity consumed. On the contrary, all the water taken by mouth is rather speedily absorbed into the blood stream. Exceptions to this rule occur, first, when the absorbing surface of the intestine, mainly the small intestine, is the seat of some inflammatory process which interferes with its normal function. This condition produces those diarrheas which are due to abnormal products of digestion or to the presence of bacteria and their toxins. In the second place, exceptions occur when there is a disordered blood supply to the intestine, for example, in ileus. Finally, exceptions occur rarely when huge quantities of water are ingested.

That the body is capable of absorbing large quantities of water without necessarily suffering therefrom is amply demonstrated in cases of diabetes insipidus, in which the daily absorption may amount to as much as 8 to 10 liters or more over long periods. Apparently as long as the elimination keeps reasonable pace with the intake no symptoms develop.

That the absorptive surface of the intestine does not refuse water even when the latter is presented in harmfully large quantities has been

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5. Rademaker, L.: The Cause and Elimination of Reactions After Intravenous Infusions, *Ann. Surg.* **92**:195-201, 1930; Reactions After Intravenous Infusions: A Further Study on Their Elimination, *Surg., Gynec. & Obst.* **56**:956-958, 1933.

6. Seibert, F. B.: Fever-Producing Substances Found in Some Distilled Waters, *Am. J. Physiol.* **67**:90-104, 1923.

observed by a number of investigators, Priestley,<sup>7</sup> MacCallum and Benson,<sup>8</sup> Miller and Williams<sup>9</sup> and Amberg and Austin.<sup>10</sup>

Rowntree<sup>11</sup> first duplicated the symptoms of water intoxication—asthenia, muscular irritability, convulsions, salivation and ultimately death—in a series of animals by administering large quantities of distilled water by mouth. He was able to relieve the symptoms both by administering saline solution and by trephining the skull. From this he concluded that the cause of death was edema, especially edema of the brain.

Helwig, Schutz and Curry<sup>12</sup> recently reported a clinical case in which they believed the death of a 50 year old woman was caused by absorption of some 9,000 cc. of tap water from the bowel within the first thirty hours after an operation for gallstones. In a series of 7 healthy young rabbits these authors were able to produce water intoxication and death by the repeated administration of 50 cc. of tap water by rectal catheter at intervals of thirty minutes. The first indication of water intoxication was the appearance of salivation after about 500 cc. of water had been given. This was followed by fine fibrillary twitchings of the ear and muscles of the extremities after the administration of about 600 cc. After about 700 cc. had been administered clonic convulsions and marked opisthotonos developed; these signs were associated with dilatation of the pupils and decreased urinary output. Death ultimately occurred in a generalized convulsion. These authors believe that the cause of death in water intoxication is cerebral edema, though Smyth, Deamer and Phatak<sup>13</sup> in 1933 explained water intoxication on the basis of alkalosis and loss of chlorides.

Of course it is a matter of everyday observation that increasing the intake of water increases the output of urine, and it is also a truism to remark that ultimately elimination must balance intake. The point

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7. Priestley, J. G.: The Regulation of Excretion of Water by the Kidneys, *J. Physiol.* **1**:304-311, 1916.

8. MacCallum, J. B., and Benson, C. C.: On the Composition of Dilute Renal Excretions, *J. Biol. Chem.* **6**:87-104, 1909.

9. Miller, J. L., and Williams, J. L.: The Effect on Blood Pressure and Non-protein Nitrogen in the Blood of Excessive Fluid Intake, *Am. J. M. Sc.* **161**:327-334, 1921.

10. Amberg, S., and Austin, R. S., cited by Rowntree.<sup>11</sup>

11. Rowntree, L. G.: (a) Water Intoxication, *Arch. Int. Med.* **32**:157-174 (Aug.) 1923; (b) The Effect on Mammals of the Administration of Excessive Quantities of Water, *J. Pharmacol. & Exper. Therap.* **29**:135-159, 1926.

12. Helwig, F. C.; Schutz, C. B., and Curry, D. E.: Water Intoxication: Report of a Fatal Human Case, with Clinical, Pathologic and Experimental Studies, *J. A. M. A.* **104**:1569-1575 (May 4) 1935.

13. Smyth, F. S.; Deamer, W. C., and Phatak, N. M.: Studies in So-Called Water Intoxication, *J. Clin. Investigation* **12**:55-65; 1933.

is that elimination certainly does not occur at equal pace with absorption under ordinary conditions but at first definitely lags behind it. Ultimately, therefore, if a balance is to result, the rate of elimination not only must equal the rate of intake but must exceed it, in order to counterbalance the initial lag. In the meantime, no less certainly, the tissues of the body must accommodate the excess of water.

That simple dilution of the blood stream is not the only mechanism involved in the storage of water is almost axiomatic. Indeed, all clinical and experimental observers agree that a portion of any considerable amount of water added to the blood stream almost immediately leaves the circulation, lodging temporarily in the fixed tissues. This is true whether the water is absorbed into the blood stream from the gastrointestinal tract or is artificially added by direct infusion of a watery solution. Clinically, such an egress of water from the blood stream to the fixed tissues of the skin and to the subcutaneous connective tissue is recognized as edema. It shows the elementary physical sign of "pitting on pressure." One would certainly surmise, even though no experimental or other evidence were available, that the skin and subcutaneous tissues are not the only tissues involved. As a matter of fact, there is much evidence that other tissues are actually involved.

It is universally agreed that after the infusion of considerable quantities of saline solution the blood volume does not long remain augmented but tends soon to return to normal. Unfortunately there exists at present no really satisfactory and accurate method of measuring the true total volume of the blood, or the true volume of either of its two constituent parts, the plasma or the cells. This is because no known method is capable of differentiating between changes due to vasomotor adjustments and changes due to transfer of fluid to or from extravascular spaces. The methods based on the use of dye are, of course, subject to gross errors, due most probably to the influence of the vasomotor mechanism on the distribution of the dye.

Simple dilution of the blood and consequent increase in its circulating volume are the first changes that follow the addition of fluid to the blood stream. Almost immediately these changes begin to be compensated by vasomotor changes tending to augment the cubic capacity of the circulatory system. As soon as dilution of the blood has occurred to any appreciable extent, however, osmotic and other relationships are undoubtedly upset. Mechanisms are then brought into play which effect a redistribution of electrolytes between the blood stream and the tissue spaces. Thus three essentially different compensatory mechanisms are operative almost immediately after an intravenous infusion has been started. To these, moreover, is very soon added a fourth, the elimination of water and salts by the kidneys and the other emunctories.

In the absence of any accurate method for examining these several mechanisms individually, conclusions as to their interrelationships and relative importance must be somewhat conjectural. Large or even huge intravenous injections fail to produce sustained elevation of the blood pressure. Moreover, the ordinary methods of computing the total blood volume fail to show an increase for moderate additions of inorganic solutions to the blood stream. Accordingly, investigators in general believe that the escape of most artificially introduced solutions from the actual blood stream is rapid.

Thus Dastre and Loye<sup>3</sup> as early as 1888 computed experimentally that 75 per cent of fluids intravenously injected in large quantities passed after a short time into the tissue spaces and serous cavities of dogs and rabbits. They adduced evidence that the tissues can store with impunity amounts of such fluids equal to from one tenth to one quarter of the total body weight.

MacCallum<sup>14</sup> in 1904 obtained up to 15 per cent of fluids intravenously injected in large volumes into experimental animals from a cannula tied into the lumen of the intestine. He thus apparently demonstrated the importance of the intestine as a water emunctory under unusual conditions.

Bogert, Underhill and Mendel<sup>15</sup> in 1916 concluded as a result of experiment that the blood volume returned to normal within thirty minutes after the injection of a quantity of saline solution equal to its computed total and within so short a time as five minutes when smaller volumes were injected.

Smith and Mendel<sup>16</sup> in 1920 injected into rabbits an amount of fluid equal to the computed normal volume of blood and observed that the bulk of the injected fluid had left the blood stream within the first five minutes. They expressed the belief that the loss of this amount of fluid could not be explained on the basis of passage of water into the muscles or cellular tissues. It must, therefore, they stated, have been extravasated into the serous cavities, the stomach and the intestine, so far as it was not excreted in the urine.

Until much more is known about the normal movements of water and chlorides in the body, and especially about the forces concerned in the movement of water between the vascular tree and the extra-

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14. MacCallum, J. B.: On the Action of Saline Purgatives in Rabbits and the Counteraction of Their Effect by Calcium, *Am. J. Physiol.* **10**:101-110, 1904.

15. Bogert, L. J.; Underhill, F. P., and Mendel, L. B.: The Regulation of the Blood Volume After Injections of Saline Solutions: Studies of the Permeability of Cellular Membranes, *Am. J. Physiol.* **41**:189-218, 1916.

16. Smith, A. H., and Mendel, L. B.: The Adjustment of Blood Volume After Injection of Isotonic Solutions of Varied Composition, *Am. J. Physiol.* **53**:323-344, 1920.

vascular spaces and between the intracellular spaces and the extracellular spaces, the ultimate significance of the portion of our experimental observations about to be described will necessarily remain in some doubt.

We have, however, estimated the distribution of water and chlorides in many of the soft tissues after the administration of an amount of 1 per cent solution of sodium chloride almost, but not quite, sufficient to cause death. The injection was stopped and the animals killed at the first suggestion of the precipitous decline in blood pressure which experience had shown immediately preceded death when an infusion was fatally large. Tissues were removed for analysis thereafter, as rapidly and gently as possible in order to minimize the factor of postmortem translocation of fluids and salts. At the same time all possible precautions were taken to prevent mechanical redistribution of blood from organ to organ or mechanical draining away of blood from cut surfaces.

The water content of the tissues was determined by drying excised, accurately weighed, minced tissues to constant weight in an oven at a temperature of 125 C.

It should be emphasized at this point that the condition of the tissues and organs which were analyzed for water and salt content was not necessarily incompatible with continued life. Though the condition was that which exists just preceding death, it was nevertheless one from which full and complete recovery is possible if the infusion is stopped exactly at this point. Repeatedly animals subjected to infusions of similar or almost similar magnitudes have recovered when the infusion has been interrupted just short of a presumably fatal dose.

As Skelton<sup>17</sup> has shown, and as appears from table 2, the water content and the mass relative to body weight of the various tissues in man and in the cat are closely similar. Presumably, therefore, similar changes in distribution of water occur in both species after massive infusions.

We have used the figures quoted by Skelton representing the weight of each organ in percentage of the total body weight, except for the various parts of the gastrointestinal tract. In this case we have used our own figures, for we have found no values in other sources. We have derived our own figures also for the normal water content of the tissues and organs, including the several portions of the gastrointestinal tract.

Our values for the gastrointestinal tract are based on analyses of 12 control cats. From these we removed the small intestine, the large intestine and the stomach. Having weighed these organs, we computed the relative weights with respect to the total body weight and thereafter

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17. Skelton, H.: Storage of Water by Various Body Tissues, *Arch. Int. Med.* 40:140-152 (Aug.) 1927.



determined the normal water content. In table 3 is summarized the relationship of the weights.

In table 4 are summarized the changes in water content of a number of tissues and organs after the infusion of a 1 per cent solution of sodium chloride in just sublethal amount. The figures presented in the first

TABLE 2—*Water Content and Mass Relative to Body Weight of Various Tissues in Man and the Cat*

Organ	Percentage of Water in Organ by Weight		Weight of Organ in Percent age of Total Body Weight	
	Man	Cat	Man	Cat
Skin .	72.03	68.3	18.0	13.94
Muscle	75.67	74.5	41.7	45.36
Skeleton	22.04	32.8	15.9	12.67
Brain. .	74.84	78.0	2.01	1.01
Liver.	68.25	67.9	2.26	2.96
Heart	79.21	78.46	0.47	0.37
Lungs.	78.96	76.3	0.69	0.51
Kidney.	82.68	75.3	0.37	0.81
Spleen	75.77	78.2	0.18	0.23
Blood	83.00	86.7	4.90	4.46
Intestine	74.54	78.3	1.81	3.40

TABLE 3—*Weight of the Separate Portions of the Gastrointestinal Tract Relative to the Total Body Weight in Cats*

Cat Number	Body Weight	Percentage of Body Weight		
		Stomach	Small Intestine	Large Intestine
1	2,610	1.30	3.82	0.58
3	2,580	1.03	3.87	0.55
4	2,680	1.41	4.50	0.92
5	2,900	0.97	2.90	0.71
6	3,010	1.16	4.50	0.61
7	3,180	0.99	2.86	0.64
8.	2,380	1.48	3.70	0.94
9	2,480	0.82	2.86	0.55
10	2,480	1.49	4.24	0.75
11	2,540	1.05	3.45	0.67
12	2,760	0.76	2.63	0.63
13..	1,860	0.83	3.44	0.77
Mean percentage of body weight		1.11	3.55	0.69
Mean percentage of body weight represented by the whole gastrointestinal tract			5.35	

\* This table shows great variation in the weight of all three parts of the gastrointestinal tract, stomach, small intestine and large intestine, expressed as percentage of the total body weight. In individual cases the values vary from as much as 30 per cent below to as much as 30 per cent above the mean for the entire group.

column are our own and are therefore not identical with the values quoted in table 2, though it will be noted that the agreement is very close.

As previously stated, the figures given in table 4 represent the distribution of water after virtually maximal intravenous infusions. It is a question whether this distribution of water is characteristic after infusions of various magnitudes or only after extremely large infusions. We have no direct evidence, but comparison of our results with those of Skelton, who estimated the distribution of water among some of the

tissues after the intravenous administration of much smaller amounts of 0.9 per cent solution of sodium chloride, shows that the order of the tissues when arranged according to their increase in water content is essentially the same for the smaller and the larger infusions. This is shown in table 5.

TABLE 4.—*Change in Water Content of Organs After Massive Infusion of 1 per Cent Solution of Sodium Chloride*

Organ	Normal Percentage of Water	Percentage of Increase in Water After Infusion
Brain.....	78.7	— 3.9 (decrease)*
Spleen.....	77.8	10.0
Skeletal muscle.....	75.0	18.4
Cardiac muscle.....	76.8	21.0
Duodenum.....	77.8	29.0
Liver.....	70.3	29.0
Kidney.....	76.6	43.5
Skin.....	57.0	57.0†
Lung.....	79.5	111.0
Pancreas.....	73.9	109.0
Salivary glands.....	72.0	119.0
Colon.....	77.0	215.0
Stomach.....	77.0	254.0

\* Under the conditions of the experiment it is questionable whether a variation of 3.9 per cent, as in the water content of the cerebrum, is significant. Nevertheless, being in the direction of decrease rather than increase, it makes it possible to state with some confidence that the cerebral tissue does not store water.

† The value for water in the skin is uncertain; not only is there a considerable normal variation in the water content of this tissue, but its fat content introduces a sizable error. The presence of fat operates to minimize any actual increase in water content, for on drying the fat does not evaporate. It thus adds to the ultimate weight of the dried tissue even though it has been entirely passive with respect to ability to hold water. The value recorded—57 per cent—was computed on the same basis as those for the other tissues. The tissue's fat content was disregarded, all possible care being exercised not to include any gross particles of fatty tissue.

In 5 cases values for water were calculated for the same animal both before and after infusion. The increase of water averaged 49.5 per cent, but this figure was not corrected for fat content.

In 2 cases in which the fat content was excluded by preliminary extraction of the tissues with ether the increase of water amounted to 38.8 per cent. In these 2 cases, however, there were no normal values as controls for the individual animals used.

TABLE 5.—*Percentage of Increase in Water Content of Organs After Large and Small Infusions of Solution of Sodium Chloride*

After Massive Infusion (500 Cc. or More per Kg. of Body Weight)— Cutting et al		After Smaller Infusion (20 Cc. per Kg. of Body Weight)— Skelton	
Blood.....	102	Blood.....	27.7
Skin.....	57	Skin.....	4.5
Liver.....	29	Liver.....	4.3
Cardiac muscle.....	21	Muscle.....	0.0
Skeletal muscle.....	18		

Although the magnitude of water stored increases with the size of the infusion as one would expect, the four tissues for which data are available store water in the same relative order. This would seem to indicate that each of these particular tissues, at least, shows a characteristic capacity for storing water, which increases to relatively the same extent in each case as more and more water is supplied.

Perhaps the gastrointestinal tract is an exception to this rule. Skelton<sup>17</sup> observed that it increased its water content by only 1.9 per cent after the smaller infusion which he used. He did not state, however, which portion of the tract was used for actual analysis. As has been previously explained, we were guided by differences in the gross appearance of the various portions of the tract at autopsy. We accordingly determined the values for separate portions of the tract and observed that the behavior of the stomach and colon differs markedly from that of the small intestine. The stomach and colon contain or store water in large amounts, whereas the small intestine contains or stores relatively little. If Skelton's figure for the gastrointestinal tract represents the small intestine only, this fact may be cited as another instance of close correlation between our findings and his. It then offers further evidence that the various tissues show characteristic behavior in the amount of water they store or contain, regardless of the absolute amount injected.

If, on the other hand, Skelton's figures represent the average capacity for storage of the gastrointestinal tract as a whole, our figures for the stomach and the colon are very much out of line. Such an interpretation would suggest that these tissues show an increasing affinity for water as the amount of infused solution increases. If the latter hypothesis is correct, there is a strong presumption that the stomach and colon take up the added water as a step in a process of excretion into the lumen of the intestinal canal, which thus acts as a safety valve. Certainly the fact that massive infusions frequently produce copious vomiting and watery purging may be considered to lend support to such a hypothesis.

The fact that the cerebrum definitely stores no water is of particular importance in view of the opinion of some investigators that when death results from water intoxication its immediate cause is cerebral edema.

Rowntree<sup>11a</sup> noted that cerebral edema was an outstanding feature in experimental animals in which water intoxication had been produced. The convulsive seizures and ultimate death of such animals could be prevented, he found, by decompressing the brain by means of openings made with a trephine in the skull.

Helwig, Schutz, and Curry<sup>12</sup> based their opinion that the dramatic features of water intoxication were due to cerebral edema largely on microscopic changes in the tissue. These changes were confined to the lungs, liver, brain, kidneys and bowel, and the most striking alteration was an acute swelling of the brain. The cerebral changes included definite widening of the perineural and perivascular spaces; vacuolation of the intercellular stroma; vacuolation, swelling and subependymal edema of the choroid plexus; vacuolation, swelling and desquamation of the ependymal lining of the ventricles, and vacuolation of the stroma of the cerebral substance.

Our observation that the cerebral substance after massive infusions does not increase its water content seems to demonstrate conclusively that whatever may be the cause of death after such infusions it is not cerebral edema. This can mean only that if the conclusions of the preceding authors are correct our animals did not die of water intoxication. Such a conclusion is not necessarily illogical, for saline solutions are not physiologically equivalent to water, even though the actual amounts of water and of saline solution which cause death may be practically identical. In all candor, however, the idea of cerebral edema as a cause of death under either set of circumstances does not seem particularly easy to reconcile with the Monro-Kellie doctrine, even in its most recently modified form.

Probably the most impressive feature observed relative to the water content of tissues after massive infusions is that it is without exception the glandular organs which show the greatest increase in water. All of these organs, the lungs, pancreas, salivary glands, colon and stomach, apparently are able to store and eliminate water against osmotic pressure gradients as at present understood. Nothing is more evident than that the distribution of water in the body after massive infusions of essentially isotonic saline solutions is not governed by any simple applications of the laws of osmosis and diffusion.

The amount of chloride in the blood and tissue was determined in these experiments by the method of Van Slyke as modified by Sunderman and Williams.<sup>18</sup> This method consists essentially of dissolving the tissues in a solution of potassium hydroxide, neutralizing this solution with nitric acid to the end point of methyl red, precipitating the chlorides with silver nitrate, digesting the mixture with strong nitric acid until all organic material has been destroyed and then titrating against potassium thiocyanate, using ferric alum as an indicator. All data on chlorides are reported in terms of grams of sodium chloride per kilogram of wet tissue.

Because the values for chloride in the tissues which we could find in the literature were unsatisfactory, we have computed all of our own values, both normal and after infusion. In table 6 are recorded the sodium chloride content of normal cat tissues, the sodium chloride content of these same tissues after massive infusions of 1 per cent solution of sodium chloride and the percentage of increase.

Of all the tissues, the skin shows the greatest variability in capacity for storing both water and sodium chloride. Its absolute value is intermediate among those for the other tissues of the body.

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18. Sunderman, F. W., and Williams, P. J.: The Analysis of Chlorides in Tissues, *J. Biol. Chem.* **102**:279-285, 1933.

Careful comparison of table 6 with table 4 shows that many of the tissues have a difference in capacity for storing the two substances. If the various tissues stored the infused solution as presented to them, viz., in the form of a 1 per cent solution of sodium chloride, the order in which the tissues appear in the two lists should be the same. The actual results are expressed mathematically in table 7.

TABLE 6.—*Normal Sodium Chloride Content of Cat Tissues and Content After Massive Intravenous Infusion of 1 per Cent Solution of Sodium Chloride*

Organ	Content in Gm of Sodium Chloride per kg of Wet Organ		
	Normal	After Infusion	Percentage of Increase
Kidney .	4.21	4.00	5.2
Liver.....	3.41	3.74	9.7
Lung . .	4.3	5.31	23.2
Duodenum	3.26	4.48	37.0
Pancreas . .	3.00	4.38	46.0
Skin.....	3.22	5.30	65.0
Muscle, cardiac	1.78	2.95	66.3
Salivary glands	2.75	4.86	76.0
Stomach ...	3.36	5.99	78.0
Spleen.....	2.51	4.86	94.0
Colon ...	2.69	5.58	107.0
Muscle, skeletal	1.05	2.42	130.0

TABLE 7.—*Evaluation of the Data Contained in Table 4 and Table 6 on the Assumption that Storage in the Tissues Is in the Form of a 1 per Cent Solution*

Organ	Gm of Sodium Chloride per Kg of Tissue		Ratio
	Theoretical	Observed	
Cerebrum	2.31	2.82	
Duodenum. ....	4.80	4.48	1 : 1.06
Muscle, skeletal.	2.60	2.42	1 : 1.08
Muscle, cardiac	3.20	2.95	1 : 1.08
Spleen	5.32	4.86	1 : 1.09
Skin	5.90	5.30	1 : 1.10
Liver	4.87	3.74	1 : 1.29
Lung	7.28	5.31	1 : 1.38
Kidney ..	6.00	4.00	1 : 1.50
Pancreas .	6.90	4.38	1 : 1.57
Stomach.	10.80	5.99	1 : 1.82
Colon..	10.85	5.58	1 : 1.86
Salivary glands	11.30	4.86	1 : 2.31

As will be noted, the cerebrum acts anomalously in that it alone appears to store sodium chloride but no water. Of the remaining tissues, the duodenum, skeletal and cardiac muscles, spleen and skin store the solution most nearly in the concentration in which it is presented to them, viz., as a 1 per cent solution. Incidentally, none of these tissues are among those which take up the most water. All the other tissues store relatively far more water than sodium chloride.

## ELIMINATION OF SODIUM CHLORIDE AND WATER

The effect of massive infusions of 1 per cent solution of sodium chloride is to increase the elimination of water by the water emunctories. Direct visible evidence occurs as follows: 1. Mucoïd material accumulates in the tracheal cannula, showing excess secretion of the tracheal and other glands of the respiratory tract. 2. Saliva drips from the mouth, nasal secretion from the nose and tears from the eyes, showing increased activity of salivary, buccal, nasal and lacrimal glands. 3. There may be copious watery dejections from the bowels, especially if the infusion is large, showing increased secretory activity of the glands of the gastrointestinal tract. 4. Vomiting or attempted vomiting almost always occurs, probably because of stimulation by excess secretion into the stomach and upper portion of the small intestine. 5. Urine is invariably evacuated in quantity, showing evidence of increased filtration by the kidneys.

Probably the other avenues of water excretion, particularly the mechanism of sensible and insensible perspiration, are affected, though we have made no attempt to collect evidence to demonstrate such activity. Although presumably all the water emunctories contribute to the elimination of the added water of a large intravenous infusion, the actual amount eliminated by all the avenues except the kidneys is not great.

During the course of our experiments, whenever an opportunity presented itself to collect vomitus, saliva or dejections, this was done, and the volumes were measured and recorded. In a number of cases in which the volumes were sufficient, chemical analyses were made for chloride content. Such observations, however, have proved difficult to evaluate for several reasons:

1. Except for occasional cases of excessive vomiting or large dejections, the amounts of secretion which have been collected have been actually very small.

2. Animals which have neither vomited nor passed stools have recovered like other animals; though we feel sure, from autopsies performed in acute experiments on other animals, that their gastrointestinal tracts contained increased amounts of secretion during the infusion, this material must have been reabsorbed during recovery and ultimately evacuated by other channels. This phenomenon apparently shows that vomiting and defecation constitute overflow mechanisms rather than essential avenues of excretion.

3. Careful analyses of the urine eliminated during the period of recovery have shown that the kidneys eliminate virtually all the sodium

chloride and by far the largest part of the water of a massive infusion within about twenty-four hours. Actually, within such a period the kidneys may eliminate more sodium chloride than was injected, and they usually eliminate more than three quarters of all the water.

TABLE 8.—*Rate of Early Elimination of Infused Sodium Chloride and Water (During the Period of Infusion)*

Cat Number	Size of Infusion (Cc. per Kg. of Body Weight)	Time in Min.	Water Eliminated (Expressed as Percentage of Amount Infused)	Sodium Chloride Eliminated (Expressed as Percentage of Amount Infused)
2B	492	85	27.0*	....
4B	550	172	32.06	....
5B	550	156	16.0	28.0
6B	725	157	31.8*	....
7B	411	74	25.0	32.0
8B	561	130	35.0*	....
9B†	427	58	9.0	10.0
10B†	439	42	7.0	9.0
16B	545	120	2.0	4.4
17B	690	150	15.7	20.5
18B	500	120	20.0	25.0
19B‡	500	122	10.0	14.0
20B	500	124	20.0	25.3
21B	408	122	14.0	16.7

\* In these animals the values were calculated on the basis of difference in weight before and after infusion; the urine was not collected.

† Animals 9B and 10B both passed copious watery stools, but the values are based solely on the urine collected.

‡ Animal 19B evacuated 130 cc. of fluid by bowel; the figures express only the elimination by kidney.

TABLE 9.—*Rate of Elimination of Infused Sodium Chloride and Water During the First Twenty-Four Hours*

Cat Number	Size of Infusion (Cc. per Kg. of Body Weight)	Time in Hours	Water Eliminated (Expressed as Percentage of Amount Infused)	Sodium Chloride Eliminated (Expressed as Percentage of Amount Infused)
5B	550	5	32	34
		20	63	95
		24.5	78	115
7B	411	5	70	95
		24	77	103
9B	427	6	47	60
		18	73	90
10B	439	5	38	48
		17	62	72
18B	500	7	47	58
		24	78	80
21B	408	7	48	50
		24	90	100

We have made a series of careful analyses of the rates of elimination of sodium chloride and water by the kidneys, which are summarized in tables 8 and 9. In table 8 appears an account of the rate of elimination of these two substances during the course of the actual infusion.

The diuretic effect of a massive infusion is shown by the kidneys within a short time after the infusion has been started, and during the actual period of administration considerable elimination occurs. During

this period the elimination of both salt and water is variable, averaging 19 per cent of all the water injected and 18.5 per cent of all the salt.

In table 9 is recorded an itemized account of the elimination of sodium chloride and water by the kidneys during the first twenty-four hours following massive infusions of 1 per cent solutions of sodium chloride.

Interesting in connection with the figures recorded in this table also is the variability of excretion of both water and sodium chloride from animal to animal, though it is by no means as great as the variability in the earlier period. The easiest explanation is to attribute such differences in rate of excretion to differences in the functioning of the kidneys, in which case we should seem to be dealing with another example of a test of renal function. We assured ourselves that the variability is actually due not to the functioning of the kidneys alone by plotting the half-hourly excretion of water and sodium chloride of three representative animals. Not only do the rates of excretion of both substances vary considerably from one half-hour to the next, but the variation is of the haphazard, unpredictable or scatter type, which indicates that the rate of excretion is governed by not one but several factors.

It is of some special interest that within twenty-four hours all the injected sodium chloride but only about 80 per cent of the water has been eliminated by the kidneys. Coller, Dick and Maddock<sup>19</sup> recently observed that when surgical patients were given moderate amounts of dextrose in saline solution intravenously for several days they showed a gain in weight. This was obviously due to a retention of water, though clinical edema did not necessarily appear. When the salt was omitted, even though the same amount of fluid as before was given, in the form of 5 per cent dextrose in distilled water, the retention disappeared, and weight was lost. Coller and his co-workers apparently made no determinations to discover whether the retention of water was associated with, or due to, a concomitant retention of sodium chloride; indeed, they failed even to discuss this matter at all. Most clinicians, in the absence of data to the contrary, probably would assume that the retention of water was secondary to the retention of chloride. The results we obtained by using massive doses of solutions of sodium chloride without dextrose seem to indicate definitely that retention of water is not dependent on retention of chloride. Indeed, the retention occurs at a time when the kidneys have excreted not only all the sodium chloride which was artificially injected but some of the salt previously present in the body. Half the animals excreted more than 100 per cent of the injected chloride within twenty-four hours.

19. Coller, F. A.; Dick, V. S., and Maddock, W. G.: Maintenance of Normal Water Exchange with Intravenous Fluids, *J. A. M. A.* **107**:1522-1527 (Nov. 7) 1936.



GENERAL ACCOUNT OF THE DISTRIBUTION AND ELIMINATION OF  
MASSIVE INFUSIONS OF SODIUM CHLORIDE AND WATER

If it now is attempted, on the basis of the figures already derived, to account for the entire bulk of solutions known to have been infused into the animals, the results are at first rather surprising.

The more bulky tissues of the body, muscles, skin, intestine, liver and skeleton, together account for about 80 per cent of the total weight of the cat, as can readily be computed from table 2. It may reasonably be assumed that the skeleton, which accounts for only about 13 per

TABLE 10.—*Storage of Water and Sodium Chloride in Muscles, Skin and Gastro-intestinal Tract After Massive Infusions \**

Cat No.	Muscle		Skin		Gastrointes- tinal Tract		Liver		Total	
	Sodium Chloride	Water	Sodium Chloride	Water	Sodium Chloride	Water	Sodium Chloride	Water	Sodium Chloride	Water
2B	....	13.8	....	4.7	....	...	....	....	....	....
4B	14.4	10.8	11.3	14.0	2.56	7.6	....	....	....	....
6B	5.4	7.1	4.0	4.4	1.22	8.7	....	....	....	....
8B	7.3	11.3	7.9	11.0	1.44	6.9	....	....	....	....
16B	15.2	10.0	....	11.7	1.24	9.7	....	....	....	....
17B	7.6	7.2	5.3	4.4	1.46	5.5	....	....	....	....
Mean	10.57	10.03	7.12	8.36	1.58	7.7	1.14†	0.15†	20.41	20.24

\* All values are expressed in percentage of the total amount infused.

† Derived from previous tables.

TABLE 11.—*The Abdominal Cavity as a Reservoir for Excess Sodium Chloride and Water*

Cat Number	Quantity Infused, Cc. per Kg.	Quantity of Abdominal Fluid at End of Infusion	Sodium Chloride Content, %	Percentage of Total Infused	
				Sodium Chloride	Water
1B	590	160 cc.	....	....	9.0
2B	492	132 cc.	....	....	13.4
3B	692	110 cc.	1.000	12.20	12.2
4B	550	130 cc.	0.950	7.50	7.8
6B	725	160 cc.	0.710	9.60	13.7
8B	561	140 cc.	0.835	7.90	9.5
17B	690	115 cc.	0.780	9.96	12.7

cent of the total body weight, is incapable of storing infused solutions because of its mechanical inexpandibility. On this assumption it appears that 80 per cent of the tissues of the body account for only about 20 per cent of the infused sodium chloride and only about 26 per cent of the infused water. The derivation of these values is shown in detail in table 10.

The only other tissue which might contribute any particular addition would be the blood, but it normally accounts for little more of the total body weight than the liver. Unfortunately, the ultimate volume after infusion being unknown, its contribution cannot be computed. However, actually the value would be negligible, for the simple reason that the figures already derived include the blood content of so great a percentage of the total mass of the body.

There are, of course, other possible storage places besides the fixed tissues, viz. the body cavities. That the abdominal cavity is an important storage place is indicated by the figures recorded in table 11. The thoracic cavity and the pericardial cavity contain only relatively insignificant amounts of fluid.

In the general accounting, of course, must be included the sodium chloride and water that have already been eliminated from the body by the kidneys. When all this has been done the balance sheet appears as follows:

	Sodium Chloride	Water
Percentage contained in 80 per cent of the fixed tissues of the body.....	19.27	26.09
Percentage contained in the abdominal cavity....	9.31	11.20
Percentage excreted by the kidneys.....	20.30	15.90
Total.....	48.88	52.19

Half of the injected fluid and salt is all that can be accounted for. The remaining 50 per cent must either have been stored in the 20 per cent of fixed tissues not subjected to analysis or have accumulated in the various body cavities other than the abdominal cavity. As previously stated the gross examination of such cavities as the intestinal canal and thoracic and pericardial cavities indicates that not much of the remaining 50 per cent of the infusion could have found lodgment in these locations. The capacity of the unanalyzed 20 per cent of the tissues of the body may be much greater than at first seems logical to suppose. The distensible connective tissues about the pancreas, between the leaves of the mesentery and in the retroperitoneal space have been reported as presenting a remarkable appearance due to gelatinous edema. Doubtless other loose, areolar connective tissues throughout the body present a similar condition which is not so evident to the naked eye. Thus the subcutaneous tissues are extensive enough to contain much of the injected fluid and sodium chloride.

It is suggested that as a result of infusion the extravascular tissue spaces are distended with water and its dissolved sodium chloride. In that case this, rather than the swelling of the cells of the tissue themselves, is the important factor in the increase in size and apparent edema of the various tissues and organs. Wherever the tissues are mechanically distensible a characteristic gelatinous edema develops. In these locations, the tissues look as if they had been simply distended with water in its ordinary free-flowing form, i. e., as if they had been infiltrated by a hypodermic needle and syringe. Nevertheless, incising them reveals the existence of the water in a peculiar jellylike state, the cut surface of the tissue presenting a sticky, viscid appearance. Such a gelatinous state is said to characterize tissue fluids normally, in contradistinction to the free-flowing character of, for instance, lymph.

## CONCLUSIONS

1. The lethal value for infusions of 1 per cent solution of sodium chloride in cats is of the order of 500 cc. per kilogram of body weight when the rate of injection is 5 cc. per kilogram of body weight per minute. This would correspond in a man weighing 154 pounds (70 Kg.) to 35 liters at a rate of 350 cc. per minute. Hypertonic solutions are lethal in smaller bulk and at slower rates of infusion.

2. During such massive infusions the blood pressure is neither greatly nor constantly affected. Vasodilatation and, particularly, diffusion of the solution into the tissue spaces serve to stabilize the blood pressure at an essentially normal level. At the time of death the blood pressure abruptly declines.

3. The important changes observed at autopsy are (a) evidences of watery vomiting and purging, (b) swelling of the entire animal, especially the abdomen, (c) the presence of a considerable amount of free fluid in the abdominal cavity, (d) edematous thickening of the stomach, the colon, and the urinary bladder, (e) gelatinous edema of the pancreas, the space between the leaves of the mesentery and the retroperitoneal space and (f) edema of the lungs and the salivary glands.

4. Unless pushed to a rather sharp end point of decompensation at which the blood pressure rapidly declines, infusions are not incompatible with rapid and complete recovery. The sharp end point is believed to represent some physiochemical imbalance rather than failure of any particular organ or system. Accidental death will occur in perhaps half the cases before any considerable amount of solution has been infused if precautions are not taken to prevent regurgitation, aspiration of the regurgitated material and ultimate drowning of the animal in its own vomitus. Pyrogenic substances contaminating the water used in compounding infusions may account for some premature deaths.

5. The relative weights of the various organs and tissues of the body and the water content of these tissues and organs are closely comparable as between man and the animals commonly used in the laboratory, specifically the cat. Experiments on the translocation of water following the administration of large intravenous infusions in the lower animals should therefore presumably be comparable with what occurs in man under similar conditions.

6. During and after a massive infusion both the water and the salt tend to leave the blood stream rapidly; they accumulate presumably in the tissue spaces. Relatively little water can be accommodated in such closely knit organs as the muscles and the skin, though because of their bulk their actual capacity for storage is considerable. Presumably the salt contained in the water thus stored is in essentially isotonic concentration. Organs such as the alimentary tract (except the duodenum).

the salivary glands and the lungs, which act to some extent as natural water emunctories, seem to store water differently. They probably do not store it passively in their tissue spaces as in the case of the organs previously mentioned, but actively within their parenchymatous cells, where they are preparing it for excretion. Accordingly, analyses show that duodenum, muscle, spleen and skin store sodium chloride and water in the proper proportions to make a 1 per cent solution. Liver, lungs, kidneys, pancreas, stomach, colon, and salivary glands, all organs concerned with the elimination of water, store water considerably in excess of the amount necessary to make a 1 per cent solution with their contained sodium chloride.

7. The cerebrum is the one tissue in the body which stores no water, though it seems to store some salt. Cerebral edema definitely does not occur after massive infusions of 1 per cent solution of sodium chloride and therefore cannot be the cause of death when the limits of toleration are exceeded.

8. Even during the course of the actual infusion of a massive quantity of 1 per cent solution of sodium chloride the kidneys eliminate a considerable amount of both the water and the salt. Before the infusion is complete nearly 20 per cent of both the water and the salt has been eliminated by the kidneys.

9. The amount of salt and water stored in tissues, amounting to approximately 80 per cent of the total body weight, for which analyses were available and the amount eliminated by the kidneys during the infusion equal about half of the total amount infused. The remaining half must have been stored in tissues constituting not more than 20 per cent of the total body weight. The most logical conclusion, in view of the spectacular gelatinous edema which was seen in the loose areolar connective tissues about the pancreas and in the retroperitoneal space, is that enormous quantities of water and salt are probably stored in these and other loose, areolar connective tissues throughout the body. These tissues, for obvious reasons, were not collected for analysis.

10. Within twenty-four hours after the administration of a just sublethal massive infusion of 1 per cent solution of sodium chloride all of the salt and about 80 per cent of the water have been eliminated by the kidneys. The rate of elimination is variable from hour to hour.

# FAT EMBOLISM

## RÉSUMÉ OF THE LITERATURE PLUS SOME NEWER THOUGHTS ON DIAGNOSIS

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Unless a subject is brought before the medical profession from time to time, it may easily slip into the background and be little thought of. Since over five hundred references to fat embolism are found in the literature, only the most striking facts concerning it will be presented in this paper. Clinically, fat embolism is difficult to substantiate conclusively. This difficulty is really not the fault of medical practitioners but is due to the nature of the disease, which makes its definite recognition difficult. Some of the newer experimental phases of its diagnosis are presented in this paper in the hope that they may be of aid to the ultimate solution of the problem.

### GENERAL SURVEY

*Historical Observations.*—As early as 1669 Lower<sup>1</sup> had injected milk intravenously in dogs, and this was probably the beginning of the knowledge of fat embolism. Magendie,<sup>2</sup> during the years 1821 to 1836, did some experimental work on hyperlipemia and its effects on the circulation in animals. His description of the experimental introduction of liquid oil into the venous circulation is classic. Zenker,<sup>3</sup> in 1862, observed the first fat emboli in the pulmonary capillaries of man after a severe crushing injury to a railroad worker. The pulmonary capillaries were seen to contain a great many emboli of fluid fat. He thought that they occurred by aspiration from the stomach through the gaping hepatic veins.

Scriba,<sup>4</sup> in 1880, reviewed all the cases up to date and then added 34 of his own. He also conducted experiments on animals and brought forth many clinical and pathologic points which had previously been

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1. Lower, cited by Flournoy, T.: *Contribution à l'étude de l'embolie graisseuse*, Paris, J. B. Baillière & fils, 1878.

2. Magendie, F.: *Leçons sur les phénomènes physiques de la vie*, Paris, J. B. Baillière, 1827, vol. 1; 1836, vol. 2.

3. Zenker, F. A., cited by Warthin, A. S.: *Internat. Clin.* 4:171. 1913.

4. Scriba, J.: *Deutsche Ztschr. f. Chir.* 12:118, 1880.

obscure. Most of the discussion of fat embolism in modern textbooks is based on the statements and conclusions which he drew. However, years have shown that some of his opinions were erroneous. Fatty embolism could be regarded as causing death in only 14 of 177 cases, and in some of these he considered the cause of death doubtful.

Lehman and Moore<sup>5</sup> (1927) by in vitro experiments showed that histamine extracted from necrotic muscles produced a rapid disintegration of the emulsified fat of normal blood serum. They concluded that fatty embolism might be readily produced in the bone marrow on a nontraumatic basis purely by the absorption of histamine from injured tissue into the blood stream. They also showed that intravenous injections of ether produce fatty embolism of the lungs by dissolving their normal emulsified fat. When the gaseous tension of the ether was lowered by evaporation in the alveoli, the free fat became visible microscopically in the blood.

*Etiology.*—The experimental work done on the causation of fatty embolism has been considerable and in many instances has led to much contradiction and confusion. Men are much more frequently affected than women, the proportion being about 8 to 1. The case of the youngest patient recorded as having fatty embolism, an infant 8 months old, was reported by Ryerson.<sup>6</sup> The age at which the condition most commonly appears is the fourth decade of life. Rarely does it occur in children, because the fat in the bone marrow is insufficient to cause it up to the fourteenth year (Speed).<sup>7</sup> Landois,<sup>8</sup> in an excellent article on the subject, stated that he found mostly palmitin and stearin in children and infants, with a smaller proportion of the more fluid olein. At body temperature oleic acid is fluid and is more easily absorbed than the more viscous palmitic and stearic acids. For this reason fatty embolism is not so common in children. It appears that alcoholic addicts are more predisposed to fatty embolism than those not so addicted. Perhaps this is due to the instability of the emulsified fat in the serum, produced by its frequent dilution with a fatty solvent after a debauch (Cubbins—personal communication).

Lehman and Moore<sup>5</sup> calculated the amount of fat in the marrow of a femur and found it to be approximately 65 cc. By experimental

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5. Lehman, E. P., and Moore, R. M.: Fat Embolism Including Experimental Production Without Trauma, *Arch. Surg.* **14**:621 (March) 1927.

6. Ryerson, E. W.: Fat Embolism in Bone Surgery: Incidence and Prevention, *J. A. M. A.* **67**:657 (Aug. 26) 1916.

7. Speed, K.: A Textbook of Fractures and Dislocations, ed. 1, Philadelphia, Lea & Febiger, 1916.

8. Landois, F.: *Deutsche med. Wchnschr.* **52**:283, 1926.

study with cottonseed oil they ascertained that if man is able to tolerate as much oil in the blood stream as a dog 120 cc. would be required for a lethal outcome. This conclusion is based on two assumptions: first, that cottonseed oil does not materially differ from the fat of the bone marrow; second, that man as well as the dog can tolerate free fat in the blood. If this is true, all the fat in the bone marrow of a femur could be well tolerated. There has been a great deal of controversy as to whether the fat is carried by the blood or by the lymph vessels. The present opinion seems to be that most of it is carried by the veins while a smaller part may be carried by the lymphatics.

It is interesting to note that experimental animals can be made to build up a resistance to experimentally induced fat embolism by repeated small injections of fat. This work was done primarily by Paul and Windholz<sup>9</sup> and later by Domanig.<sup>10</sup> They noted that such animals could withstand many times the lethal dose. No droplets of fat could be found free in the blood serum of these animals. Evidently such droplets are rapidly destroyed by a newly formed unknown substance.

*Pathogenesis and Pathologic Picture.*—After an injury to the fat of the bone marrow or adipose tissue, fat is liberated by the disintegration of the supporting fibrous tissue. Naturally there are ruptured blood vessels in the vicinity of the injury. The arteries squirt more blood into the area, thereby increasing the pressure, while the veins remain open and absorb the fatty mixture by venous suction (Miloslavich<sup>11</sup>), particularly if its consistency is more or less fluid. Gauss<sup>12</sup> brought out the point that fatty embolism is more common with fracture than with any other condition because the veins are encased in a bony wall. Hence they cannot collapse as elsewhere in the body but remain wide open for the admittance of the fatty mixture. This process may take place immediately or proceed for some time until coagulation occurs. This pathologic condition involves all the organs of the body and is too well known by all to be discussed in this brief résumé.

Lehman and McNattin<sup>13</sup> noted that fatty embolism is present in the lungs of about 50 per cent of unselected cadavers. These men have conclusively shown that anatomically the diagnosis of fatty embolism

9. Paul, F., and Windholz, F.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. 38:614. 1925.

10. Domanig, E.: Deutsche Ztschr. f. Chir. 236:693, 1932.

11. Miloslavich, E. L.: Wisconsin M. J. 29:139, 1930.

12. Gauss, H.: Pathology of Fat Embolism, Arch. Surg. 9:593 (Nov.) 1924.

13. Lehman, E. P., and McNattin, R. F.: Fat Embolism: II. Incidence at Postmortem, Arch. Surg. 17:179 (Aug.) 1928.

as the cause of death cannot be safely made. Wright<sup>14</sup> observed fat embolism in 52 of 100 consecutive patients examined post mortem, the majority of whom did not suffer from fracture or contusion as a result of a fall or some other accident. He also helped to substantiate the contention that postmortem observations of fat embolism are not pathognomonic evidence of violence.

Carrara<sup>15</sup> noted fat embolism in 22 per cent of cases of cardiovascular-renal disease and 44 per cent of cases of burn. Catsaras<sup>16</sup> reported fatty embolism in the lungs of 18 out of 67 patients with postinfluenzal pneumonia. To add to the already great confusion on the subject, acidosis, phlegmonous gastritis, acute pancreatitis, chronic tuberculosis, menstrual suppression, hepatitis, splenitis and tuberculous pneumonia, in fact, almost all diseases, poisonings and infections to which the body has been subjected, have been reported in the literature as having caused fat embolism at one time or another. Vance,<sup>17</sup> in 1931, wrote a comprehensive paper on fat embolism from a pathologic point of view, which is a classic in the present literature on the subject.

*Symptoms.*—There is no clinical correspondence between the apparent injury and the degree of resulting hyperlipemia. Injuries apparently identical may in one person be followed by a fatal hyperlipemia and in another cause but a slight disturbance.

The onset may be sudden, within a few hours of the injury, but usually does not become manifest until the third or fourth day. Once the symptoms set in, they may vary from a slight irritability and excitability of the patient to maniacal periods associated with high grade delirium, and death. If the symptoms are watched carefully, it is seen that they have a tendency to be cyclic. The cycle corresponds to the passage of the emboli from the pulmonic circulation to the systemic and their gradual return. Many patients with hyperlipemia appear to be doing nicely when gradually they begin to show signs of nervousness and excitability. At this time the pulse rate and temperature begin to show a slight rise. The rate of respiration shows a more rapid rise than that of the pulse, and even early in the development of the symptoms it may be dyspneic. As more capillaries are obstructed in the lungs, the dyspnea increases correspondingly. Cyanosis may or may not appear, according to the extent of pulmonary impairment. Gradually a passive congestion occurs in the lungs and moist rales are audible over the bases. A cough begins to

14. Wright, R. B.: *Ann. Surg.* 96:75, 1932.

15. Carrara, M.: *Friedreich's Bl. f. gerichtl. Med.* 49:241, 1898.

16. Catsaras, J.: *Presse méd.* 28:618, 1920.

17. Vance, B. M.: *Significance of Fat Embolism*, *Arch. Surg.* 23:426 (Sept.) 1931.



appear and is of a productive nature, rarely bringing up blood-stained sputum, however. For this reason, in many of the cases the diagnosis is bronchopneumonia.

As the pulmonary arterial pressure increases, the heart must beat faster in order to overcome the circulatory resistance. The pulse rate becomes faster and stronger, and the blood pressure begins to rise. If the resistance in the pulmonic circulation increases or remains great, the heart before long begins to weaken. Its rate increases while its force decreases. The blood pressure correspondingly begins to fall. If some of the emboli lodge in the coronary vessels, the cardiac failure comes on much more quickly. Before long, the pulse becomes imperceptible, the arterial pressure falls, the venous pressure rises and the picture of deep shock and cardiac failure appears. The temperature varies from subnormal to 106 or 107 F., according to whether or not the heat-regulating center is disturbed by the emboli. The usual temperature during the height of the disease is about 103 F. In the terminal stage the temperature often rises much higher.

Petechial hemorrhages (Ryerson,<sup>6</sup> 1916) may appear in the skin, as in any other disease in which the embolic phenomena predominate. However, because the capillaries are not actually occluded, as in bacterial endocarditis, but the circulation is greatly slowed by the increased viscosity of the blood (Gauss<sup>18</sup>), they are rare. LeCount and Gauss<sup>19</sup> reported on 14 cases of death following fatty embolism in which autopsies had been done. A study of the clinical symptoms in these cases is instructive, as it gives us some idea of what occurs in cases of milder involvement which does not have a fatal outcome.

All of the patients in these cases passed from consciousness to a restless stage. In 12 this took the form of delirium, 11 becoming so violent as to require restraint. Eleven passed from delirium to the comatose state. In all 14 dyspnea was present with an associated increase in respiratory rate, the average being 53 respirations per minute. Cheyne-Stokes respiration developed in 2 cases, air hunger in 4 and a marked cough in 2. The pulse became weak and shallow and showed an average rate of 153 per minute. Involuntary passage of urine and feces occurred in 12 cases, and in the other 2 the records were incomplete. At the time of the patient's admission to the hospital the temperature was either normal or subnormal; it then rose considerably (to an average of 105.2 F. for the 14 cases). The time that the patients lived varied from two to seventeen days, with an average of six days.

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18. Gauss, H.: Studies in Cerebral Fat Embolism, *Arch. Int. Med.* 18:76 (July) 1916.

19. LeCount, E. R., and Gauss, H.: *Tr. Chicago Path. Soc.* 9:251, 1915.

*Diagnosis.*—In the majority of cases of fat embolism the condition is so mild that it does not cause symptoms or so severe that death results in a few days from involvement of the lungs or the brain. During life the diagnosis of fat embolism is justified only if there is a history of an injury and of the typical clinical manifestations. The incubation period varies from a few hours to three or four days from the time of the accident. ~~It is a good point to remember Dennis' rule in this respect, in spite of the exceptions: shock, three hours; fat embolism, three days; pulmonary embolism, three weeks. (Speed?)~~

Additional confirmatory signs are the presence of fat in the urine, the occurrence of fat emboli in the retinal vessels as demonstrated by the ophthalmoscope and the appearance of petechial hemorrhages in the chest, shoulders and neck. ~~The presence of the large circular cells of Elting and Martin<sup>20</sup> or the fat globules of Warthin<sup>21</sup> in the sputum is not a pathognomonic sign, as they are found in conditions other than fat embolism.~~ As a rule, fat embolism is rarely diagnosed from clinical signs and symptoms; it is most often discovered accidentally at necropsy. In the differential diagnosis delirium tremens, fracture of the skull, bronchopneumonia and shock must be most seriously considered.

*Prognosis.*—The prognosis of fatty embolism should always be reserved, because some of the patients who appear to be progressing satisfactorily die suddenly. As to expectation of life, most of the patients recover, but because in only the fatal or very serious attacks is the diagnosis made and the mild attacks are overlooked, most people have the reverse opinion.

*Treatment.*—As fatty embolism associated with fracture is not of common occurrence and is rarely diagnosed when it does occur, one can understand why the literature on the treatment of this complication is not illuminating. Gröndahl<sup>22</sup> stated that a terminal result occurs in but 1 of every 3,000 cases and that death following fracture can be attributed to fatty embolism in only 1 per cent of the cases. Much experimental work has been done on the prophylaxis, with forethought and logical thinking. Wells,<sup>23</sup> Ryerson<sup>6</sup> and Caldwell and Huber<sup>24</sup> have shown that the use of a tourniquet during an operation or manipulation reduces to a minimum the possibility of the development of fatty embolism. This is true especially if the tourniquet is allowed to remain

20. Elting, A. W., and Martin, C. E.: *Ann. Surg.* **82**:336, 1925.

21. Warthin, A. S.: *Internat. Clin.* **4**:171, 1913.

22. Gröndahl, N. B.: *Deutsche Ztschr. f. Chir.* **111**:56, 1911.

23. Wells, H. G., cited by Ryerson.<sup>6</sup>

24. Caldwell, G. T., and Huber, H. L.: *Surg., Gynec. & Obst.* **25**:650, 1917.

in place for an hour after the operation. Simonds<sup>25</sup> observed that etherized dogs are more susceptible to fatty embolism than are those anesthetized by substances which do not dissolve fat. This is a point of some importance, and if an anesthetic which is not a solvent of fat can be used as efficiently and safely it should be given preference.

Warthin<sup>21</sup> advised the following prophylactic management:

1. Avoidance of unnecessary or rough handling of patients.
2. Immediate splinting and early reduction of all fractures (Tanton<sup>26</sup>).
3. Use of a saw in preference to the chisel in orthopedic operations, if possible (Lexer<sup>27</sup>).

4. Slow removal of Esmarch's bandage (Buerger<sup>28</sup> and Aberle<sup>29</sup>). Reiner<sup>30</sup> advised canaliculizing the vein, allowing the first blood after removal of the constrictor to flow out. Czerny<sup>31</sup> and fifty years later Wegelin<sup>32</sup> advocated intravenous injection of sodium carbonate, probably with the idea of forming a soluble soap. This method has fortunately received but little support. All experimental animals died under this regime. The active treatment of this condition is very poor, and many of the suggested methods are not only theoretically but practically in error.

Czerny<sup>31</sup> advised venesection to lessen the venous congestion. Schanz<sup>33</sup> stated the belief that physiologic solution of sodium chloride administered both intravenously and by hypodermoclysis is of benefit. Bissell,<sup>34</sup> however, expressed the opinion that such a procedure is contraindicated because of increased pressure on the right side of the heart. Wilms<sup>35</sup> suggested drainage of the thoracic duct. Fritsche<sup>36</sup> observed experimentally that this procedure is beneficial if done at the first appearance of the symptoms. Gröndahl<sup>22</sup> noted that even ligation of the femoral vein and removal of the inguinal glands did not prevent fatty embolism. Wilms<sup>35</sup> advised incising the area of fracture and

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25. Simonds, J. P.: A Study of Low Blood Pressures Associated with Peptone Shock and Experimental Fat Embolism, *J. A. M. A.* **69**:883 (Sept. 15) 1917.

26. Tanton, J.: *J. de chir.* **12**:287, 1914.

27. Lexer, E.: *Lehrbuch der allgemeinen Chirurgie*, ed. 3, Stuttgart, Ferdinand Enke, 1908.

28. Buerger, L.: *Vrtljschr. f. gerichtl. Med. (Supp.)* **39**:159, 1910.

29. Aberle, R.: *Ztschr. f. orthop. Chir.* **19**:89, 1907.

30. Reiner, M.: *München. med. Wchnschr.* **54**:2004, 1907.

31. Czerny, V.: *Berl. klin. Wchnschr.* **12**:593, 1875.

32. Wegelin, C.: *Schweiz. med. Wchnschr.* **4**:133, 1923.

33. Schanz, A.: *Zentralbl. f. Chir.* **37**:43, 1910.

34. Bissell, W. W.: Amount of Fat in the Blood Stream of Persons with Broken Bones, *J. A. M. A.* **67**:1926 (Dec. 23) 1916.

35. Wilms, M.: *Semaine méd.* **30**:138, 1910.

36. Fritsche, E.: *Deutsche Ztschr. f. Chir.* **107**:456, 1910.

combating the origin of fatty embolism by evacuating the blood and fat. Pituitary preparations, caffeine, coramine (pyridine betacarboxylic acid diethylamine in a 25 per cent solution), morphine and sympatol (the tartrate of paramethylaminoethanol phenol) have been suggested in the active treatment, as they have been seen both experimentally and clinically to produce a steady fall in the quantity of fat in the blood.

VALUE OF CHEMICAL ANALYSIS OF THE BLOOD AND PHYSICAL  
MEANS OF DETERMINING THE QUANTITY OF FAT

Since the problem of fat embolism has to do with the presence of droplets of fat in the blood stream, it was thought that quantitative determinations of fat in the blood would be of material aid in its diagnosis. For this reason the known methods were looked up and studied in great detail. Kumagawa and Suto<sup>37</sup> described a saponification method in 1908. Bang<sup>38</sup> in 1918 described an extraction method, which however is not accurate enough to be truly scientific. Bloor, Pelkan and Allen<sup>39</sup> first brought the nephelometric method to the foreground in 1922. Later, in 1928, Bloor<sup>40</sup> published an account of an improvement on this method. Stoddard and Drury<sup>41</sup> described a titration method in 1929.

After a careful study, counsel was sought from several well known physiologic chemists, and all agreed that it is beyond the ability of the average part time chemist to carry out these methods with perfect accuracy. Even when the determinations are done in well equipped laboratories by properly trained men, the variations are so great as to render them of no real diagnostic value. For the present at least, the outlook along these lines is unfavorable. Clinical investigation in the serologic department of the Cook County Hospital has revealed many blood serums of almost creamlike appearance. These were from patients suffering from diabetic coma, persons with lipoid nephrosis and lactating women. In spite of the fat content of the blood having reached this startling height, these patients revealed no manifestations of fat embolism. Some investigators have noted in cases of diabetic coma that the concentration of total lipoids in the blood has reached 26 per cent (Bantin<sup>42</sup>), although the normal concentration is only 0.4 per cent.

37. Kumagawa, M., and Suto, K.: *Ztschr. f. Biochem.* 8:212, 1908.

38. Bang, I.: *Biochem. Ztschr.* 91:224, 1918.

39. Bloor, W. R.; Pelkan, K. F., and Allen, D. H.: *J. Biol. Chem.* 52:191, 1922.

40. Bloor, W. R.: *J. Biol. Chem.* 77:53, 1928.

41. Stoddard, J. L., and Drury, P. E.: *J. Biol. Chem.* 84:741-1929.

42. Bantin, C. F.: *Diabetic Lipemia Retinalis and Fat Embolism*, J. A. M. A. 86:546 (Feb. 20) 1926.

These observations, therefore, have conclusively proved to me that it is not the total fat content of the blood in which one should be interested, but the state in which this fat occurs. If it is in the form of a stable emulsion, no fat droplets are present in the blood, and therefore no embolism can occur. On the other hand the corpuscular fat content is of all importance, as it causes the occlusion of the vessels which produces the embolic phenomena. Unfortunately, only 5 per cent of the total fat content of the blood is found in this form. If one considers that the total fat content, as has been stated before, is only 0.4 per cent, one realizes that corpuscular percentage almost approximates zero. Therefore, it stands to reason that any total chemical method for determining increases or decreases of this substance would be far beyond the scope of quantitative chemical determinations, as the percentage of error introduced by the best present day methods would be too great.

Other fields of experimental work were sought for possible aid in determining the fat content of the blood. The use of the spectroscope was suggested. However, both a physicist and an excellent physiologist stated that the concentration of fat was too small to produce any appreciable variations. At a later date the possibility of measuring electric conductivity in order to determine changes in the fat content of the blood serum was discussed. This method as well as the use of the polariscope received negative comment and was abandoned.

#### RESULTS OF DARK FIELD EXAMINATIONS OF THE BLOOD IN CASES OF RECENT FRACTURE AND IN CONTROL CASES

Edmunds<sup>43</sup> first described the dark field examination of the blood for particles of fat in 1877. Further work along these lines was carried on by Neumann<sup>44</sup> in 1907. Gage and Fish<sup>45</sup> in 1924 published a most excellent article on this subject, describing investigative work on absorption and assimilation of fat in the lower animals. The senior author was the first to give the microscopic particles of fat in the blood the name of chylomicrons (1920), meaning that they are 1 micron in diameter and are composed of chyle.

A control study of 25 miscellaneous blood serums from the medical wards of the Cook County Hospital was undertaken. No variations from the normal were found. Several creamlike specimens of blood from a lactating woman yielded a few interesting observations. In spite of a cholesterol content of 335 mg. per hundred cubic centimeters and

43. Edmunds, J.: *Monthly Micr. J.* 18:78, 1877.

44. Neumann, A.: *Zentralbl. f. Physiol.* 21:102, 1907.

45. Gage, S. H., and Fish, P. A.: *Am. J. Anat.* 34:1, 1924.

a milky serum, no actual droplets of fat could be seen, a phenomenon which shows the marvelous stability of the emulsion of the blood serum.

As the average blood cell is 10 microns in diameter, it has been estimated that in order to occlude the finer capillaries of the lung the droplet of fat must be at least 12 to 15 microns in diameter. In none of the control cases were droplets of this size noted. In order to show the feasibility of this diagnostic method in cases of embolism, olive oil was injected intravenously into a dog. Five cubic centimeters was injected slowly. Two minutes later, with a clean syringe and needle, a cubic centimeter of blood was removed from the leg opposite to that in which the injection had been made. When a drop of this blood was examined under the dark field, ameba-shaped droplets of olive oil, at least twice the diameter of an erythrocyte, could be easily demonstrated.

#### TECHNIC OF ANALYSIS OF URINE IN CASES OF FAT EMBOLISM

In the study of this problem, I have examined several hundred specimens of urine for the presence of fat in suspected cases of fat embolism. After a period of time, it was observed that this apparently simple investigative phase of the problem presented an interesting physical phenomenon. Since this phenomenon heretofore has evidently not been emphasized, its investigation was undertaken. That fat is excreted by the kidneys in the urine of patients suffering from fat embolism is well known and often spoken of in the literature. But unfortunately the detection of fat in the urine is difficult because of one very elementary physical phenomenon. The droplets of fat float on the surface of the urine and therefore are not excreted from the bladder unless the last few cubic centimeters of urine are expressed. For this reason in many cases in which the urine contains fat, the specimens examined give negative results because this simple fact is overlooked. Jirka and I,<sup>46</sup> in 1936, conclusively showed this, both in vitro and in clinical cases. Oleic acid was injected into the pelvis of the kidney after a retrograde pyelogram had been made. It was noted several hours later that all of the injected oil could be collected from the last few cubic centimeters of urine, while the remaining 200 to 400 cc. of urine was free from fat.

#### A CONTROL STUDY OF THE URINE AND BLOOD OF PATIENTS WITHOUT EMBOLISM

Until Jirka and I<sup>47</sup> took up the study of cases of nontraumatic conditions, no investigation of the urine and blood in such cases was ever carried on. An examination of 200 miscellaneous specimens of

46. Jirka, F. J., and Scuderi, C. S.: *J. Lab. & Clin. Med.* 20:631, 1935.

47. Jirka, F. J., and Scuderi, C. S.: *J. Lab. & Clin. Med.* 20:945, 1935.

urine and blood in the Cook County Hospital failed to reveal a single instance of droplets of free fat in the centrifuged specimen of either the urine or the blood. Eleven of the specimens of blood showed chylous emulsion, but it was physiologic, for the blood had been drawn within an hour or two after the ingestion of a fatty meal. We next studied fluids obtained in 50 cases of fracture from one to one hundred and forty-four hours after the accident. In not a single instance were we able to find any free fat droplets in specimens of either the urine or the blood.

From the work just described it may be safe to assume that the presence of droplets of fat (larger than a chylomicron) in specimens of either the urine or the blood is indicative of free intravascular fat, which is consistent with fat embolism. However, the examination of these liquids requires long centrifuging, staining of the supernatant liquid with sudan III and careful study of the fluid. Many trials are necessary before one learns the technic.

#### THE VALUE OF ROENTGENOGRAMS OF THE CHEST IN THE DIAGNOSIS

In an attempt to bring further aid to the diagnosis of this condition, Jirka and I<sup>48</sup> proved by experimental work on dogs that roentgenograms of the chest show definite changes in the lungs after intravenous injection of oil. This work will be carried on in human beings when the opportunity presents itself. As far as I know, the roentgen ray has never been used as an aid to the diagnosis of fat embolism. For this reason I am presenting for the first time an evaluation of the use of roentgenograms of the chest for this purpose. Eleven dogs were used in the experiments, animals weighing close to 12.5 Kg. being selected whenever possible. Sterile oleic acid was given intravenously to 6 and sterile olive oil to 5 of the animals. Varying doses were used. One must not lose sight of the fact that fat embolism is not a true embolism in the sense of a permanent occlusion of a vessel. It is simply a retardation of the flow of blood through a capillary while the droplets of oil become elongated and are slowly forced from the arterial to the venous side of the circulation.

#### CONCLUSIONS

1. It has been demonstrated conclusively that a diagnosis of the embolism can be made during life by the use of modern diagnostic methods.

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48. Jirka, F. J., and Scuderi, C. S.: Fat Embolism: An Experimental Study on the Value of Roentgenograms of the Chest in Diagnosis, *Arch. Surg.* 33:708-713 (Oct.) 1936.

2. Quantitative determinations of fat in the blood are of no value in the diagnosis, because the physiologic variations are too great.

3. Qualitative dark field examinations of the blood should be of great aid in the diagnosis, in the hands of trained microscopists.

4. In the examination of the urine in suspected cases, only the last few cubic centimeters of catheterized specimens are valuable.

5. Intravascular droplets of fat if present in sufficient quantity will always produce changes in the lungs detectable in roentgenograms.

6. Experimentally it has been shown that dogs can be made immune to many times the lethal intravenous dose of liquid fat by repeated increasing doses. Whether an emulsifying or digestive ferment develops is not clear. Although the thought is perhaps fantastic at this time, it may be said that should clinicians be able to diagnose the condition with definite accuracy, many lives might be saved by the development of an emulsifier or digestive ferment for this disease.



# NORMAL ANATOMY AND VARIATIONS OF THE PERIPHERAL NERVES OF THE LEG AND FOOT

APPLICATION IN OPERATIONS FOR VASCULAR DISEASES:  
STUDY OF ONE HUNDRED SPECIMENS

M. THOMAS HORWITZ, M.D.

PHILADELPHIA

The treatment of obliterative vascular disease by peripheral nerve block was first reported by Silbert<sup>1</sup> (1922), the posterior tibial nerve having been blocked with alcohol for relief of pain in thromboangiitis obliterans. Carlette<sup>2</sup> (1929) reported his method of cutting the terminal sensory branches subcutaneously above a painful ulcer of the malleolus. Smithwick and White<sup>3</sup> (1930) reported 11 cases in which alcohol was injected and Allen<sup>4</sup> (1932) 29 cases from the same clinic in which similar treatment was employed. In 1933 Laskey and Silbert<sup>5</sup> reported on 18 patients treated by the division and immediate suture of the peripheral nerves. The procedure was recommended to avoid sloughs due to spilling or seepage of alcohol and because occasionally the entire sensory nerves were not blocked by means of alcohol. Smithwick and White<sup>6</sup> (1935) reported a total of 45 cases; in the later ones the block was effected by crushing the nerves rather than by injecting alcohol. The nerves were crushed for a distance of  $\frac{1}{4}$  inch (0.6 cm.) if regeneration within three months was desired and of  $\frac{1}{2}$  inch (1.3 cm.) if anesthesia was to be prolonged for six months.

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From the Daniel Baugh Institute of Anatomy, Jefferson Medical College.

1. Silbert, S.: A New Method for the Treatment of Thrombo-Angiitis Obliterans, *J. A. M. A.* **79**:1765 (Nov. 18) 1922.

2. Carlette, C. E.: A Rapidly Curative Operation for Irritable Ulcer of the Malleolus, *Surg., Gynec. & Obst.* **48**:811, 1929.

3. Smithwick, R. H., and White, J. C.: Elimination of Pain in Obliterative Vascular Disease of the Lower Extremity, *Surg., Gynec. & Obst.* **51**:394, 1930.

4. Allen, A. W.: Results Obtained in the Treatment of Raynaud's Disease by Sympathetic Neurectomy and in Thrombo-Angiitis Obliterans by Desensitization of Peripheral Sensory Nerves, *Ann. Surg.* **96**:867, 1932.

5. Laskey, N. F., and Silbert, S.: Thrombo-Angiitis Obliterans, *Ann. Surg.* **98**:55, 1933.

6. Smithwick, R. H., and White, J. C.: Peripheral Nerve Block in Obliterative Vascular Disease of the Lower Extremity, *Surg., Gynec. & Obst.* **60**:1106, 1935.

The following points have been uniformly noted:

1. The anesthetized area is also sympathectomized and the increased circulation of the part may be determined visibly, palpably and instrumentally. This increase is due to the fact that the vasoconstrictor fibers lie intermingled with the sensory components of the peripheral nerves.<sup>7</sup> The resultant elevations in the temperature of the surface may approach the maximum rise obtained with spinal anesthesia (Smithwick and White).

2. Pain is controlled; frequent dressings become possible; necrotic detritus may be debrided, and healing is accelerated.

3. The anesthetized area becomes dry, and loss of heat from the surface of the skin is thus diminished.

4. The procedure has reduced the number of major amputations and increased the number of minor operations and the number of patients treated successfully without operation.

5. Results have proved more satisfactory in cases of thromboangiitis obliterans than in those of arteriosclerosis.

6. A marked rise in temperature may be taken as an indication of the potential efficiency of a lumbar sympathetic ganglionectomy.

The advised operative technic consists of the exposure of the sensory nerves that supply the involved areas of the foot, one at a time and at intervals of several days to a week, through small incisions, avoiding lateral dissection of the tissues, large vessels, the use of tooth forceps, rake retractors and hemostats, and omitting suturing of the deep tissues and the fascia. Silk sutures are introduced through the skin without the aid of forceps and tied loosely with perfect approximation of the edges of the skin. In a case of thromboangiitis obliterans a careful dissection of the nerve from the remaining components of the neurovascular bundle becomes a technical difficulty.

Although impressed with the rational basis of the procedure and the enthusiastic reports of it by the previously mentioned contributors, I have noted that its application in some cases resulted in rapidly increasing necrosis and gangrene. This result was seemingly due in great part to excessive dissection necessitated by difficulty in finding the nerves, which were not located at the sites recommended by the various authors. A perusal of these authors' description reveals occasional inadequacy of descriptive detail, and from my study of anatomy I feel that in some instances slightly different approaches are preferable or advisable. A survey of many of the standard textbooks and dis-

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7. Kuntz, A.: *The Autonomic Nervous System*, Philadelphia, Lea & Febiger, 1929.

secting manuals, English, French and German, reveals not infrequently an incongruity and inadequacy of detail in discussion of the sensory nerves of the lower extremity.

In the belief that the maximum benefit by this method is obtained only by location of the nerve with the least possible trauma, I undertook the study of (a) the most conservative approach for each sensory nerve of the foot and (b) the most constant anatomic location of each nerve at a site above the terminal (sensory) divisions and below all important motor divisions. For this investigation 70 lower extremities were carefully studied, many of which were dissected with the cooperation of members of the freshman class. The proper surgical approach and the principles suggested by these studies were applied on 30 additional specimens, so that a total of 100 lower extremities were investigated.

#### SAPHENOUS NERVE

*Average Diameter, Course and Relations.*—The average diameter of the saphenous nerve is  $\frac{3}{8}$  inch (0.3 cm.). It is the real terminal branch of the femoral nerve. It accompanies the femoral artery to the hiatus in the adductor muscle, passes along the tendon of the adductor magnus to the medial side of the knee joint and pierces the fascia lata near the tendon of the sartorius muscle. It passes downward subcutaneously behind the medial border of the tibia just posterior to the great saphenous vein, giving off the medial crural cutaneous branches to the skin of the medial and anterior surfaces of the leg. It divides into two branches, of which the smaller continues along the margin of the tibia to the ankle while the other passes in front of the internal malleolus. The latter is then distributed to the skin on the medial side of the foot and extends as far as the medial side of the great toe, anastomosing with the medial branch of the superficial peroneal nerve.

*Branches and Their Variations.*—In 89 of the specimens examined the nerve divided into its two terminal branches 6 inches (15 cm.) above the internal malleolus. The larger branch left the medial border accompanied by the internal saphenous vein, to cross anteriorly 4 or 5 inches (10 to 12.5 cm.) above the internal malleolus. Of the remaining 11 cases, the terminal branching occurred 5 inches (12.5 cm.) above the internal malleolus in 5, 3 inches (7.5 cm.) above in 3 and 2 inches (5 cm.) above in 3.

*Sensory Distribution and Most Constant Site.*—The nerve therefore supplies the surface of the medial and anterior aspects of the calf and leg and the medial surface of the instep and of the ball of the big toe (fig. 1). The most constant site was noted to be 7 inches (18 cm.) above the internal malleolus at the medial border of the tibia, posterior

or posteromedial to the internal saphenous vein and superficial to the deep fascia (figs. 2 *A* and 3 *A*).

*Surgical Approach.*—A 1 inch (2.5 cm.) incision is made, its center 7 inches (18 cm.) above the tip of the internal malleolus just medial to the inner border of the tibia. First the vein is located in the subcutaneous tissue, and the nerve is found directly posterior or posteromedial to it (fig. 3*A*).

#### POSTERIOR TIBIAL NERVE

*Average Diameter, Course and Relations.*—The average diameter of the posterior tibial nerve is  $\frac{1}{4}$  to  $\frac{3}{8}$  inch (0.6 to 1 cm.). It is the main branch of the sciatic nerve and represents its continuation. It

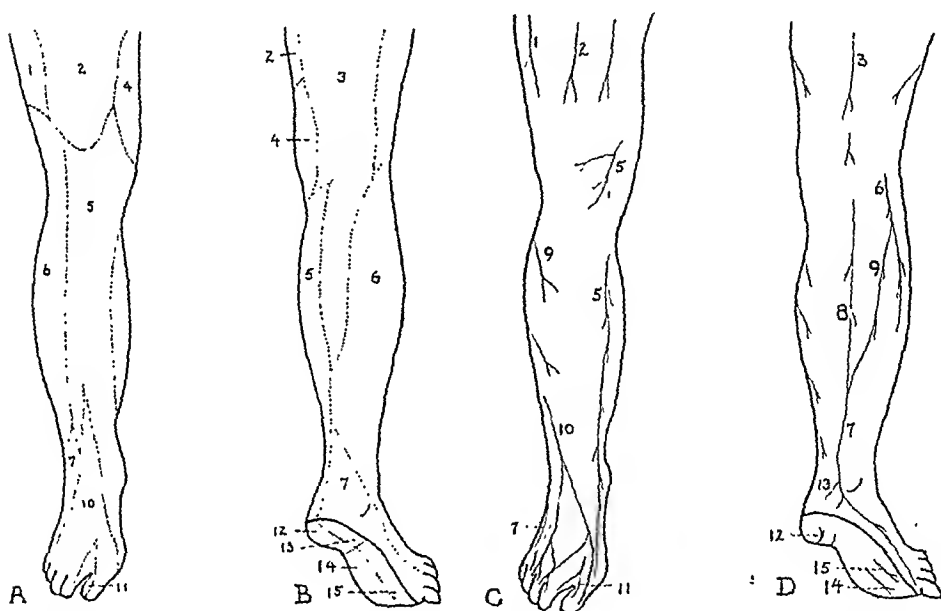


Fig. 1.—*A* and *B*, cutaneous sensory areas of the lower extremity. *C* and *D*, sensory nerve distribution of the lower extremity. The nerves are indicated as follows: 1, lateral femoral cutaneous; 2, anterior femoral cutaneous; 3, posterior femoral cutaneous; 4, cutaneous branch of the obturator; 5, internal or long saphenous; 6, lateral sural cutaneous; 7, sural; 8, medial sural cutaneous; 9, peroneal anastomotic; 10, superficial peroneal; 11, deep peroneal (anterior tibial); 12, internal or medial calcaneal rami; 13, external or lateral calcaneal rami; 14, medial plantar, and 15, lateral plantar.

gives off muscular branches in the thigh and passes through the popliteal fossa, lying lateral to and behind the popliteal vein. It accompanies the posterior tibial division of the popliteal artery, lying first on its medial side and then crossing behind the artery and descending along its lateral surface. Anteriorly lie the tibialis posticus and the flexor

digitorum longus muscles, the lower part of the tibia and the posterior ligaments of the ankle joint; posterior are the gastrocnemius and soleus muscles above and the deep fascia below. Anterior to the ligamentum laciniatum, between the internal malleolus and the medial prominence

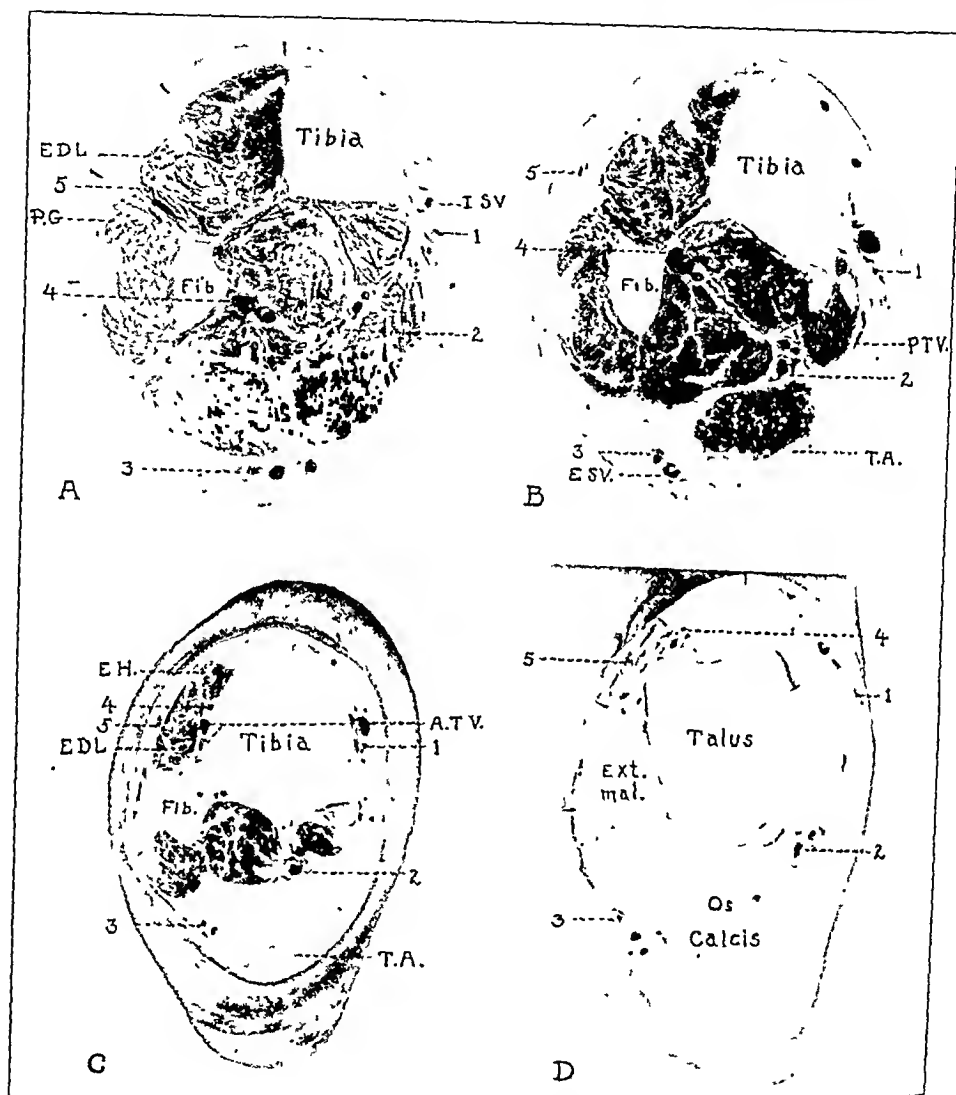


Fig. 2.—Cross sections made (A) 6 inches (15 cm.) above the internal malleolus, (B) 3 1/2 inches (89 cm.) above the internal malleolus, (C) 1 1/2 inches (38 cm.) above the internal malleolus and (D) at the level of the tip of the internal malleolus. The nerves are indicated as follows. 1, saphenous; 2, posterior tibial; 3, sural, 4, anterior tibial, and 5, superficial peroneal. I.S.V. indicates the internal saphenous vein, E.S.V. the external saphenous vein, P.T.V. the posterior tibial vessels, A.T.V. the anterior tibial vessels, EDL the extensor digitorum longus, P.G. the peroneal muscle group, T.A. the achilles tendon and E.H. the extensor hallucis longus. Note the superficial peroneal nerve in A, the saphenous nerve in A, the posterior tibial nerve in B, the sural nerve in B and the anterior tibial nerve in C and D.

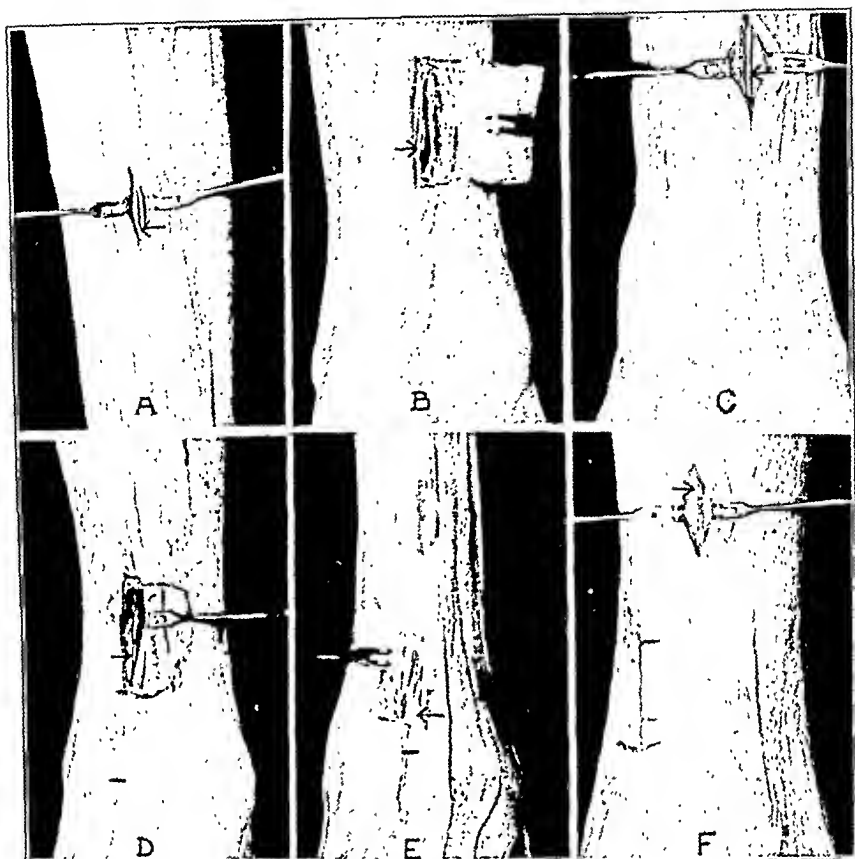


Fig. 3.—Surgical approaches to the peripheral nerves. Nerves are indicated by arrows. (The use of rake retractors and the dissection of flaps are contraindicated but practical here for demonstrative purposes.) *A*, saphenous nerve. One inch (2.5 cm.) incision made 7 inches (18 cm.) above the internal malleolus. The nerve lies posteromedial (shown to the left) to the internal saphenous vein at the medial border of the tibia. *B*, posterior tibial nerve. One and one-half inch (3.8 cm.) incision made at the medial border of the achilles tendon and 3 inches (7.5 cm.) above the internal malleolus. From lateral to medial (left to right) are the medial border of the achilles tendon, the nerve, the posterior tibial artery and venae comites and the flexor digitorum longus muscle. *C*, sural nerve. One inch (2.5 cm.) incision made at the lateral border of the achilles tendon, 4 inches (10 cm.) above the external malleolus. *D*, anterior tibial nerve. One and one-half inch (3.8 cm.) incision made  $2\frac{1}{2}$  inches (6.4 cm.) above the ankle joint (marked). From medial to lateral (left to right) are the tibialis anticus muscle, the anterior tibial artery, the nerve and the extensor hallucis longus and the extensor digitorum longus muscle. *E*, anterior tibial nerve. One inch (2.5 cm.) incision made 1 inch (2.5 cm.) above the ankle joint (marked). From medial to lateral (left to right) are the tibialis anticus and the extensor hallucis longus muscle, the anterior tibial artery and venae comites, the nerve and the medial tendon of the extensor digitorum longus muscle. *F*, superficial peroneal nerve. One inch (2.5 cm.) incision made anterolaterally 5 inches (12.5 cm.) above the external malleolus. The nerve lies subcutaneously in the groove between the peroneal group of muscles and the extensor digitorum longus.

of the calcaneus, the nerve divides into its plantar divisions  $\frac{1}{2}$  to 1 inch (1.3 to 2.5 cm.) proximal to the division of the artery.

*Branches and Their Variations.*—Muscular branches arise in the popliteal space and extend to the triceps surae, popliteus and plantaris muscles and to the tibialis posticus, flexor digitorum longus and flexor hallucis longus muscles below the fossa.

The terminal plantar nerves are formed  $\frac{1}{2}$  inch (1.3 cm.) above and behind the tip of the internal malleolus. The smaller posterior division immediately gives off the medial calcaneal branch or branches. In 4 cases this branch arose from the posterior tibial nerve directly, in 3 coming off 1 inch (2.5 cm.), and in the fourth 3 inches (7.5 cm.), above the site of terminal division. In 4 instances the posterior tibial nerve was split for a distance of 2 inches (5 cm.), 3 to 4 inches (7.5 to 10 cm.) above the internal malleolus, by a small twig off the posterior tibial artery.

The medial plantar nerve divides into muscular and cutaneous twigs and digital branches to the skin of the plantar surface of the medial aspect of the big toe and adjacent surfaces of the second, third and fourth toes. The lateral plantar division supplies the remaining part of the fourth and fifth toes by its superficial branch; the deep division gives off muscular and articular twigs.

*Sensory Distribution and Most Constant Site.*—The nerve therefore supplies the cutaneous surface of the medial part of the heel and the plantar surface of the foot and toes (fig. 1). The most constant site is 3 inches (7.5 cm.) above the tip of the internal malleolus, directly in the line of the medial border of the achilles tendon and at a depth of  $\frac{3}{4}$  inch (1.9 cm.), anterior to the deep fascial covering of the flexor digitorum longus (figs. 2 B and 3 B).

*Surgical Approach.*—A 1 to  $1\frac{1}{2}$  inch (2.5 to 3.8 cm.) incision, its center 3 inches (7.5 cm.) above the tip of the medial malleolus, is made in line with the medial border of the achilles tendon. At a depth of  $\frac{3}{4}$  inch (1.9 cm.) the fascia posterior to the flexor digitorum longus is incised and the nerve is exposed lateral to the posterior tibial artery and its venae comites, the largest component of this neurovascular bundle (fig. 3 B).

#### SURAL NERVE

*Average Diameter, Course and Relations.*—The average diameter of the sural nerve is  $\frac{1}{8}$  inch (0.3 cm.). Its medial cutaneous branch arises from the tibial nerve in the popliteal space, runs down the calf in the groove posterior and between the two heads of the gastrocnemius muscle with the small saphenous vein. At the middle of the leg it pierces the crural (deep) fascia, joining with the peroneal anastomotic branch of the lateral sural cutaneous nerve shortly thereafter to form

the sural nerve. The latter descends anterolateral to the small saphenous vein between the lateral third and the medial two thirds of the belly and tendon of the gastrocnemius muscle. It leaves the latter to cross behind the lateral malleolus to the dorsum of the foot.

*Branches and Their Variations.*—The lateral sural cutaneous nerve comes off the common peroneal nerve in the popliteal space and supplies the calf and the lateral part of the leg. The medial sural cutaneous and peroneal anastomotic branches meet any distance from the midportion of the leg to 4 inches (10 cm.), usually 6 inches (15 cm.), above the external malleolus to form the sural nerve. In only one case was the origin higher—3 inches (7.5 cm.) below the fibular head.

In 98 cases the sural nerve divided  $\frac{1}{2}$  inch (1.3 cm.) behind and above the tip of the external malleolus into two branches, a small posterior one, the lateral calcaneal branch, and a large anterior branch. The latter passed to the dorsum of the foot, ramified with the intermediate cutaneous division of the superficial peroneal nerve and terminated as the lateral digital branch of the fifth toe. An additional lateral calcaneal branch came off the sural nerve 2 inches (5 cm.) above the external malleolus.

*Sensory Distribution and Most Constant Site.*—The nerve therefore supplies the lateral surfaces of the leg, ankle, heel, foot and fifth toe (fig. 1). The most constant site is 4 inches (10 cm.) above the tip of the external malleolus just at the lateral border of the achilles tendon. Here is the external saphenous vein, and the nerve is located anterolateral to it, both lying superficial to the deep fascia (figs. 2 B and 3 C).

*Surgical Approach.*—A 1 inch (2.5 cm.) incision is made, its center 4 inches (10 cm.) above the tip of the external malleolus, at the lateral border of the achilles tendon. If not found immediately, the nerve will be found lying anterolateral to the external saphenous vein (fig. 3 C).

#### DEEP PERONEAL (ANTERIOR TIBIAL) NERVE

*Average Diameter, Course and Relations.*—The average diameter of the deep peroneal nerve is  $\frac{1}{16}$  to  $\frac{1}{8}$  inch (0.1 to 0.3 cm.). It is mainly motor. Together with the superficial peroneal nerve, it passes between the two heads of the peroneus longus and then pierces the extensor digitorum longus muscle and comes to lie in the crural interosseous space, lateral to the anterior tibial artery. In the upper part of the leg it lies between the extensor digitorum longus and the tibialis anticus muscle and in the middle of the leg, between the extensor hallucis longus and the tibialis anticus. Then it crosses behind the extensor hallucis longus, and in the lower part of the leg for 1 to 2 inches (2.5 to 5 cm.) above the ankle joint it lies between this muscle



and the extensor digitorum longus laterally. At the ankle it divides into a medial and a lateral branch.

In 95 cases the nerve lay lateral to the artery and its venae comites in the upper and middle parts of the leg, then passed anterior to the artery 4 inches (10 cm.) above the ankle joint and in the lower 2 inches (5 cm.) of the leg again lay lateral or anterolateral to the vessel. In 4 cases the nerve was lateral, then passed posterior to the artery and then medial to it, while in 1 case it lay lateral, then anterior and then medial to the anterior tibial artery.

Sabotta and McMurrich illustrated the nerve as coursing at first lateral, then posterior and then medial to the artery and its venae comites. Testut, Morris (ninth edition) and Gray (twenty-first edition) illustrated the nerve as first lateral, then anterior and then medial to the artery. As already noted, the former relation occurred in 4 cases and the latter in only 1 case, and these should not be represented as anatomic normalities but rather as infrequent variations.

*Branches and Their Variations.*—The nerve divides into two terminal branches. In all the cases in this series except 2 this division occurred  $\frac{1}{2}$  inch (1.3 cm.) above the ankle joint. In one of the exceptional cases it occurred  $2\frac{1}{2}$  inches (6.4 cm.) above, and in the other at the level of, the astragalotibial joint. The medial branch lies lateral to the dorsalis pedis and at the base of the first interosseous space pierces the deep fascia to supply articular twigs, muscular twigs to the first interosseous muscle and cutaneous branches to the contiguous surfaces of the great and second toes. The lateral branch supplies articular branches and muscular twigs to the extensor digitorum brevis muscle.

*Sensory Distribution and Most Constant Site.*—The nerve supplies only the dorsal contiguous surfaces of the first and second toes (fig. 1). The most constant site is 1 inch (2.5 cm.) above the astragalotibial joint anteriorly beneath the cruciate crural ligament, and between the extensor hallucis longus muscle medially and the extensor digitorum longus laterally. It lies lateral or anterolateral to the anterior tibial artery and its venae comites.

A less constant site is  $2\frac{1}{2}$  inches (6.4 cm.) above this joint, between the extensor hallucis longus muscle laterally and the tibialis anticus medially. Here the nerve lay anterior to the artery and its venae comites in 96 of the cases and posterior in 4 (figs. 2 C and D and fig. 3 D and E).

*Surgical Approach.*—A 1 inch (2.5 cm.) incision is made, its center 1 inch (2.5 cm.) above the ankle joint anteriorly at the juncture of the outer two thirds and medial third of the surface of the skin of the anterolateral quadrant of the leg (fig. 2 D). The cruciate crural

ligament is slit, the medial tendon of the extensor digitorum longus retracted laterally, the tendon and belly of the extensor hallucis longus drawn medially and the nerve exposed as it lies anterolateral or lateral to the artery and its venae comites. In 5 cases it was found medial to the artery (fig. 3 E).

The following, less desirable approach may be utilized if gangrene is ascending the dorsum of the foot to make the approach just described inadvisable. A 1 to 1½ inch (2.5 to 3.8 cm.) incision is made, its center 2½ inches (6.4 cm.) above the ankle joint anteriorly just lateral to the readily palpable tendon of the tibialis anticus muscle. The transverse crural ligament is slit, the tendon of the tibialis anticus retracted medially and that of the extensor hallucis longus laterally. Beneath the belly of the latter lies the neurovascular bundle on the anterolateral surface of the tibia. In this exposure the nerve was found anterior or anterolateral in 96 cases and posterior in 4. The nerve is easily lifted away from the artery, unlike the venae comites, which are bound to the vessel by tough fibrous strands (fig. 3 D).

#### SUPERFICIAL PERONEAL NERVE

*Average Diameter, Course and Relations.*—The average diameter of the superficial peroneal nerve is ⅛ inch (0.3 cm.). It is formed, with the deep peroneal nerve, by the division of the peroneal nerve behind the head of the fibula, after the latter nerve perforates the peroneus longus muscle. The superficial branch leaves between the two heads of the muscle and courses down the leg on its outer aspect, covered by the peroneus brevis. In the lower third of the leg it pierces the crural (deep) fascia, dividing into the medial and intermediate dorsal cutaneous nerves, which are distributed over the dorsum of the foot to the toes.

*Branches and Their Variations.*—The nerve pierced the crural (deep) fascia, to become subcutaneous 5 inches (12.5 cm.) above the tip of the external malleolus in 90 cases in this series. In 10 cases it exited elsewhere—6 inches (15 cm.) above the tip of the external malleolus in 1, 3 inches (7.5 cm.) above in 5, 2 inches (5 cm.) above in 2 and 4 inches (10 cm.) above in 2.

The division of the nerve into its two branches was usually found 2½ inches (6.4 cm.) above the external malleolus. In 3 cases the division occurred below and in 5 cases above this point, the highest division occurring 5 inches (12.5 cm.) above the external malleolus, at the site of exit of the nerve through the deep fascia.

The medial branch supplies the medial part of the dorsum of the foot dividing into two branches, one to the medial side of the big toe and the other to adjacent sides of the second and third toes. The inter-

mediate division supplies the intermediate portion of the dorsum of the foot, dividing into two branches. One supplies the adjacent surfaces of the third and fourth toes; the other terminates in the fourth and fifth toes and anastomoses with the sural nerve.

*Sensory Distribution and Most Constant Site.*—The nerve therefore supplies the anterior surface of the lower one third of the leg and the region of the ankle, the medial and intermediate parts of the dorsum of the foot and the dorsum of all the toes except the adjacent surfaces between the first and second toes (fig. 1). The most constant site is 5 inches (10.5 cm.) above the tip of the external malleolus, just within the anterior border of the fibula, in the groove between the peroneal group of muscles and the extensor digitorum longus. The nerve was found exiting through the crural (deep) fascia and lying in the subcutaneous tissues in 91 of the cases. In 9 cases the nerve was found beneath the deep fascia (figs. 2 *A* and 3 *F*).

*Surgical Approach.*—A 1 inch (2.5 cm.) incision is made, its center 5 inches (12.5 cm.) above the tip of the external malleolus and in the palpable groove between the peroneal group of muscles and the extensor digitorum longus. This site is at the juncture of the lateral third and the medial two thirds of the surface of the skin of the anterolateral quadrant of the leg (fig. 2 *A*). The nerve was found subcutaneously in 91 of the cases. If the nerve is not located, the deep fascia is to be incised, for it lay deeply in 9 cases (fig. 3 *F*).

# CALCIFICATION AND OSSIFICATION IN TUBERCULOMA OF THE BRAIN

REVIEW OF THE LITERATURE AND REPORT OF THREE CASES

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LOS ANGELES

The intracranial lesions which come to be the seat of calcareous deposits or bony formation vary remarkably in nature and location. Calcification of the pineal body and of the choroid plexus and formation of bone in the dura and in its reduplications seem to be the result of regressive change and are of no clinical importance. On the other hand, roentgenograms of the skull of a patient who has presented symptoms and signs of increased intracranial pressure or of some localized lesion occasionally disclose an abnormal shadow cast by calcareous or osseous deposits. As demonstrated in a series of over 600 cases of intracranial tumor in which autopsy was done, which were studied in the Cajal Laboratory, calcification is most likely to occur within a true neoplasm. In a few instances, however, the lesion has turned out to be of some other character, such as a calcified tuberculoma. Three examples of calcified or ossified tuberculoma which came to our attention have been made the subject of special study. Certain interesting facts pertaining to the general problem of calcification and formation of new bone, which have hitherto not been stressed, have thereby come to light. We have recorded our observations and reviewed the reported cases which we were able to find. It was our purpose to study the incidence and behavior of these healed tuberculomas, to investigate the histologic character of the calcareous or osseous deposits within their borders and to determine the possible significance of these phenomena.

Regardless of its location, the formation of a tubercle is the result of a reaction of nonimmune tissues to the tubercle bacillus or, more strictly speaking, to its waxy content. The stages through which the tubercle passes depend somewhat on the type of organism and on the ultimate degree of resistance of the host. If the disease proves

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to be rapidly progressive, the reactive phases of the tubercle—encapsulation, fibrosis, calcification and ossification—are not observed, the lesion showing only central caseation. On the other hand, when the process of healing occurs it is accompanied by some or all of these characteristic changes. These evidences of bodily reaction do not necessarily mean complete quiescence of the lesion. Local or general spread of the disease may take place within the cranial space, as elsewhere, even after more or less complete healing has taken place.

The behavior of tuberculous infection in the intracranial and intraspinal spaces varies considerably in different cases. In most instances the lesion occurs in the form of leptomeningitis. Whether in such cases the miliary tubercles represent the primary lodgment of bacilli as a result of blood stream infection (as in generalized miliary tuberculosis) or, as some have argued, a secondary spread from some pre-existing tubercle is of no vital moment in this connection.<sup>1</sup>

In a smaller number of cases autopsy discloses one or more discrete tubercles lodged in the substance of the brain, with or without miliary tubercles in the leptomeninges. The tubercles may be small, in which case they are often multiple and at times numerous. Occasionally, however, a large solitary mass is found which is capable of provoking an increase in intracranial pressure. Patients with such a lesion not infrequently come to operation with a diagnosis of intracranial tumor, and the surgeon may be entirely unaware of the nature of the lesion until the microscope makes it clear.

Certain pathologic characteristics of tuberculomas of the brain should be emphasized. It is of interest that while they may be found in any or all parts of the brain they tend to develop in the cerebral or cerebellar cortex, probably because of the more abundant blood supply of this structure. The tendency of solitary tubercles to be situated in the cerebellum is as yet unexplained.<sup>2</sup> True caseation, with its characteristic softening, is never found in tuberculomas of the brain; instead there is

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1. It has seemed to us that the theory that tuberculous meningitis is due to a secondary spread of infection from a preexisting tubercle lacks something to make it entirely convincing. The presence of a tubercle is not a priori evidence that the new infection has come from this source. On the other hand, the presence of cerebral tubercles of different sizes in certain instances suggests that "showers" of organisms have reached the brain on several different occasions. Further, observations in such cases do not indicate that the infection has spread concentrically about the primary tubercle, as usually happens when leptomeningitis is consequent to surgical interference with a gross tuberculoma. On the contrary, the miliary nodules are clustered primarily about the branches of the middle cerebral arteries, which strongly suggests that the organisms arrived by these channels. The subject needs further study before it can be considered closed.

2. Ehlers, H., and Courville, C. B.: *Solitary Tuberculoma of the Cerebellum*. Bull. Los Angeles Neurol. Soc. 1:81, 1936.

solidification of necrotic tissue, even in the absence of fibrous connective tissue. This is perhaps a result of the peculiarities of the cerebral blood supply or the effect of some unusual reaction of the brain to the bacillus.

#### INCIDENCE OF CALCIFICATION AND OSSIFICATION IN TUBERCLES OF THE BRAIN

The actual incidence of calcification or formation of bone in intracranial tuberculomas must be very low. In most instances the patient dies of tuberculous meningitis or of the effects of increased intracranial pressure before calcification can take place. In other words, in most cases either the progressive character of the lesion itself or the malignant nature of the attendant meningitis precludes the possibility of those changes in the tuberculoma which favor calcification or ossification. Garland and Armitage<sup>3</sup> noted the incidence of tuberculoma as shown by 13,000 autopsies. Eighty-nine tuberculomas were observed at these autopsies; in 2 cases (2.51 per cent) the lesion was calcified. The incidence as observed at autopsy is therefore extremely low (0.014 per cent). In a collected series of 815 cases of tuberculoma reported in the literature, Scott and Graves<sup>4</sup> noted only 11 instances of calcification (1.3 per cent). The relative infrequency of these healed lesions was further stressed by Stewart,<sup>5</sup> who stated that examples are few and far between. Freeman<sup>6</sup> stated that healed tubercles are of questionable existence, although he reported 2 calcified cortical lesions which he thought might be of tuberculous origin. In a series of 1,000 cases of intracranial tumor observed in Cushing's clinic, Van Wagenen<sup>7</sup> found but 14 instances of tuberculoma. None of these lesions was said to be calcified.

In a survey of 13,839 reports of autopsies, Rasdolsky<sup>8</sup> found 32 cases of tuberculoma of the brain. In only 1 case was calcification present in a tuberculoma.

Our own figures may be of interest in this connection. In a series of 15,000 autopsy records were listed 405 cases of tuberculous meningitis

3. Garland, H., and Armitage, G.: *Intracranial Tuberculomata*, J. Path. & Bact. **37**:461, 1933.

4. Scott, E., and Graves, G. O.: *Tuberculoma of Brain: Report of Four Cases*, Am. Rev. Tuberc. **27**:171, 1933.

5. Stewart, M. J.: *Healed Tuberculoma of the Cerebellum*, J. Path. & Bact. **30**:577, 1927.

6. Freeman, W.: *Neuropathology: The Anatomical Foundation of Nervous Diseases*, Philadelphia, W. B. Saunders Company, 1933, p. 174.

7. Van Wagenen, W. P.: *Tuberculoma of the Brain: Its Incidence Among Intracranial Tumors and Its Surgical Aspects*, Arch. Neurol. & Psychiat. **17**:57 (Jan.) 1927.

8. Rasdolsky, I.: *Tuberkulome des Gehirnes*, Ztschr. f. d. ges. Neurol. u. Psychiat. **154**:18, 1935.

and 43 cases of tuberculoma of the brain. In 3 cases the tuberculomas were either calcified or calcified and ossified. The incidence of "healed" tubercles in our series would therefore be 1 in 5,000 miscellaneous cases (0.02 per cent), 1 in 135 cases of tuberculous meningitis (0.7 per cent) and 1 in about 15 cases of tuberculoma of the brain (6.6 per cent).

#### REVIEW OF THE LITERATURE

In a study of intracranial tumor published in 1864, Ogle<sup>9</sup> reported 2 calcified tuberculomas in 75 cases of calcified tuberculous lesion collected over a period of twenty-two years. Lancereaux and Lackerbauer<sup>10</sup> reported a case of calcified tuberculoma in the left optic thalamus; the lesion had apparently been present for over sixty years. In Foà's case<sup>11</sup> a calcified tuberculoma, apparently quiescent, was found in the left cerebellar hemisphere of a 12 year old boy who died of nephritis. The first case in which a diagnosis of calcified tuberculoma was made roentgenographically was that of Klieneberger.<sup>12</sup> The diagnosis was never verified. In a discussion of the roentgen aspects of the problem, Ström<sup>13</sup> described a case in which the diagnosis was verified surgically and cited the cases of Siemon<sup>14</sup> and Sabat.<sup>15</sup> Another case in which the lesion was discovered by roentgen examination (post mortem) was that described by Stewart.<sup>5</sup> Other cases in which the diagnosis was verified by operation or by roentgen examination were described by Marie, de Martel and Behague,<sup>16</sup> Cushing,<sup>17</sup> Paterson and Stevenson<sup>18</sup> and Vincent,

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9. Ogle, J. W.: Cases Illustrating the Formation of Morbid Growths, Deposits, Tumors, Cysts, etc., in Connection with the Brain and Spinal Cord, and Their Investing Membranes, *Brit. & For. M.-Chir. Rev.* **34**:457, 1864.

10. Lancereaux, E., and Lackerbauer, M.: *Atlas d'anatomie pathologique*, Paris, G. Masson & fils, 1871, p. 395.

11. Foà, P.: Tubercolo cerebellare guarito, *Gior. d. r. Accad. di med. di Torino* **9**:403, 1903.

12. Klieneberger, Carl: Die Radiographie intracranieller Prozesse in der inneren Medizin, mit besonderer Berücksichtigung der radiographisch darstellbaren Hirntumoren, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **14**:106, 1909.

13. Ström, S.: Ueber die Röntgendiagnostik intrakranieller Verkalkungen, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **27**:577, 1919-1920.

14. Siemon, G. S.: Ausgedehnter Defect und teilweise verknöchert Tumor der linken Grosshirnhemisphäre, Atrophie der rechten Kleinhirnhemisphäre und der linken Olive, *Inaug. Dissert.*, Marburg, 1893; cited by Ström.<sup>13</sup>

15. Sabat: Aus der Röntgendiagnostik der Erkrankungen des Kopfes und der Wirbelsäule, *Verhandl. d. deutsch. Rönt.-Gesellsch.* **9**:101, 1913; cited by Ström.<sup>13</sup>

16. Marie, P.; de Martel, and Behague, P.: Ablation d'un tubercule intracranien: Guérison du malade, *Rev. neurol.* **36**:1109, 1920.

17. Cushing, H.: The Intracranial Tumors of Preadolescence, *Am. J. Dis. Child.* **33**:551 (April) 1927; *Intracranial Tumours*, Springfield, Ill., Charles C. Thomas, Publisher, 1932, pp. 114-115.

18. Paterson, J. E., and Stevenson, W. D. H.: Case of Healed Tuberculoma of the Brain: Operative Removal, with Pathological Report, *Glasgow M. J.* **113**: 281, 1930.

Heuyer and Vogt.<sup>19</sup> In all these cases the patients were reported to be alive at the time the articles were published, which speaks for complete quiescence of the lesion. The lesion was extirpated in all cases except that of Cushing, in which only suboccipital decompression was done for a cerebellar tuberculoma which subsequently became progressively calcified. In the cases of Smith<sup>20</sup> and of Borchardt<sup>21</sup> the diagnosis was verified at autopsy.

The essential details of the reported cases are included in the table.

In this series of 18 reported cases (including 3 of our own) of calcified tuberculoma of the brain, the lesion was single in 15 instances and multiple in 3. There seemed to be no site of special predilection. Diagnosis was made ultimately by autopsy in 10 cases, by operation in 6 cases and by roentgen examination in 2 cases.

The quiescence of calcified or ossified tubercles is evidenced by the patients' long periods of survival (over sixty years in the case of Lancereaux and Lackerbauer<sup>10</sup>) and by the fact that in 6 cases (33.3 per cent) the patient was still living at the time the report was made, from one and a half to eleven years after the condition had been diagnosed. Surgical extirpation was not followed by tuberculous meningitis, a disease which often occurs after removal of noncalcified tuberculomas of the brain. Death may result from the spontaneous development of tuberculous meningitis in such cases, however (cases of Foà<sup>11</sup> and Borchardt<sup>21</sup> and our own case 3). A fatal issue may be due also to increased intracranial pressure and exhaustion (our case 1), to internal hydrocephalus (our case 2), to status epilepticus (?) (case 2 of Ogle<sup>9</sup>), to Addison's disease (Stewart<sup>5</sup>) or to other related (pulmonary tuberculosis in our case 2) or unrelated (uremia in the case of Lancereaux and Lackerbauer<sup>10</sup>) causes.

#### REPORT OF CASES

CASE 1.—*Vomiting and left hemiplegia in a boy of 8 years; recent enlargement of the head, aphasia and progressive impairment of auditory and visual acuity; admission in coma; calcified mass in right parietal lobe shown in roentgenogram; death; autopsy; large calcified tubercle in right parietal lobe.*

A Mexican boy aged 8 years was admitted to the Los Angeles County Hospital on Jan. 13, 1931. He was then in a state of coma. The parents stated that at the age of 3 years the patient began to have attacks of headache and vomiting associated with unsteadiness of movement; these continued for four years. For the

19. Vincent, C.; Heuyer, G., and Vogt, C.: Tubercle pariéto-occipital opéré depuis 3 ans, *Rev. neurol.* 2:880, 1933.

20. Smith, R. P.: Large Calcified Tuberculoma of Cerebrum with Independent Terminal Cerebral Hemorrhage, *J. Path. & Bact.* 30:583, 1927.

21. Borchardt, J.: Verkalkte Solitär-tuberkel im Gehirn bei tuberculöser Meningitis, *Arch. f. Kinderh.* 99:181, 1933.



# Calcification and Ossification in Tuberculoma of the Brain

Author	Age	Sex	Pathologic Observations	Source of Infection	Comment
Ogle, 1861 (case 1)	36	F	Calcified tuberculoma in velum interpositum; ventricles distended, ependymal granulations; thickened arachnoid	Shoulder and lungs	Symptoms for 1 mo.
(case 2) .....					
Lancereux and Lackerbauer, 1871	65	M	Calcified tuberculoma size of hazelnut in right cerebellar lobe	Not stated	Epileptiform convulsions
Simon, 1895 (quoted by Strom)	?	?	Calcereous tuberculoma size of hazelnut in left optic thalamus	Lungs	Right hemiparesis since age of 4 yr.
Simon, 1895 (quoted by Strom)	?	?	Calcified tuberculoma 1.5 by 2.5 by 2 cm. in ventral part of frontal lobe; bony formation and calcareous crystals demonstrated histologically	Not stated	
Font, 1903	10	M	Calcified tuberculoma deep in left cerebellar hemisphere; meningitis; slight hydrocephalus	Not stated	
Shunt, 1909 (quoted by Strom)	17	?	Calcified tuberculoma size of walnut in inferior portion of right frontal and parietal lobes	Not stated	Jacksonian fits and hemiplegia on left
Klenczberger, 1909 1910	12	M	Calcified tumor in region of corpora quadrigemina (diagnosed as tuberculoma by roentgenogram and tuberculin test)	Unknown	
Ström, 1919 1921	21	F	Calcified tuberculoma size of plum in left frontal lobe, verified by operation; calcareous material and bony formation shown microscopically	Unknown	Symptoms for 13 yr.
Marle, de Martel and Dehugue, 1920	18	M	Tuberculoma size of mandarin orange in left frontal lobe, verified by operation; microscopic demonstration of calcareous material in tubercle	Tuberculous glands in cervical region	Jacksonian convulsions, paralysis of right arm; alive after operation
Stewart, 1927	27	M	Calcified tuberculoma size of hazelnut in right cerebellar lobe; demonstrated by roentgenogram after death, verified at autopsy	Tuberculous glands of cervical region	Death from Addison's disease
Smith, 1927	62	M	Tuberculomas in right cerebral hemisphere and lenticular nucleus; calcareous material demonstrated microscopically	Unknown; mother died of tuberculosis	"Stroke" at 4½ yr.; dragged left foot, tremor right hand
Cushing, 1927	14	M	Progressive calcification of tuberculoma exposed at operation; not verified histologically	Pulmonary tuberculosis	Intracranial pressure; alive 7 yr. after operation
Patterson and Stevenson, 1930	16	M	Tuberculoma of right parietal lobe; calcareous material demonstrated microscopically	Pulmonary tuberculosis	Convulsions at 2 and 5 yr.; mental symptoms at 13; still alive after operation
Vincent, Heuyer and Vogt, 1933	5	M	Tuberculoma size of hazelnut in right parieto-occipital region; roentgen and histologic demonstration of calcification; tissue removed at operation	Not stated; father died of tuberculosis	Symptoms for 6¾ yr.; alive 32 mo. after operation
Horchardt, 1933	7	M	Four small conglomerate tuberculomas, exact location not stated; calcification demonstrated roentgenographically and histologically	Pulmonary tuberculosis	Symptoms for 4¾ yr.; died of tuberculous meningitis
Ivans and Courville, 1938 Case 1	5	M	Large calcified tuberculoma 6 by 7.5 cm. in right parieto-occipital region; demonstrated roentgenographically before death	Pulmonary tuberculosis	Symptoms of increased pressure, aphasia and left hemiplegia for 5 yr.
Case 2.	10½	M	Calcified tuberculoma 3 by 1.3 by 0.7 cm. in right frontal lobe; noncalcified tuberculoma in left cerebellar hemisphere	Tuberculous tracheobronchial lymph nodes	"Tuberculous meningitis" at 7 yr.; general convulsions at 10 yr.
Case 3 ..	6	..	Calcified and ossified tuberculomas in right frontal lobe (1 by 0.5 cm.) and left frontal and parietal lobes (2 to 6 cm.)	Probably pulmonary tuberculosis	Listlessness and irritability for 3 wk. before death

\* In all the cases the diagnosis was verified at autopsy unless otherwise stated

past year there had been gradually progressive weakness of the left arm and leg. For nine months there had been marked increase in fluid intake and output. The patient's head had noticeably enlarged for five months. There had been rapid loss of vision and hearing for three months, and the boy had been completely deaf and blind for about two months. He had been in a comatose state for sixty hours before admission.

The child was born by precipitate delivery. Shortly before the onset of illness he sustained a minor injury to the head, which was probably of no significance. During the past three years he had acquired a peculiar antipathy for sweets.

The boy was deeply comatose. The skin, which was darkly pigmented and covered with sudamina, was tightly drawn over the emaciated trunk and extremities. There was an increased amount of hair over the body. The head was much larger than normal, the parietal bosses being particularly prominent. The occipitofrontal circumference of the head was 21 inches (53.3 cm.), and the suboccipitobregmatic circumference was  $21\frac{1}{2}$  inches (54.6 cm.). The percussion note was high pitched, and a well defined cracked pot sound could be elicited. The head and eyes were turned to the right. Coarse bubbling rales were heard over the entire chest. There was some lagging of the left side, associated with dulness of the percussion note on this side.

The pupils were widely dilated and reactionless. The left was slightly larger than the right. A rotatory nystagmus was constantly present. The optic disks were small and pale and presented a fairly sharp margin. The vessels were small and somewhat tortuous. The cup was filled in. The left arm and leg were rigid in a position of complete extension and internal rotation. The right arm was rigid in flexion; the right leg was less rigid and could be moved within narrow limits. The deep reflexes were entirely absent throughout. On the right Babinski's sign and Chaddock's sign were elicited; on the left the extension rigidity prevented any plantar response.

A roentgenogram of the skull taken two days after the patient's admission disclosed a calcified mass about 4 cm. in diameter in the right posterior parietal region. All the suture lines of the cranial vault were widely spread. There was marked convolutional atrophy of the inner table of the skull (fig. 1).

The child died on January 30 with signs of bronchopneumonia.

An autopsy was performed by Dr. Sidney R. Garfield twelve and one-half hours after death. Pleural adhesions were noted at the apex of the right lung and over the posterior portions of both lungs. A small caseous and calcified nodule about the size of a pea was observed at the base of the right lung. The tracheo-bronchial lymph nodes also were calcified and necrotic. The myocardium was flabby. The liver was congested and showed cloudy swelling. The spleen was slightly enlarged and congested. The pancreas was hard and fibrous. The bladder was distended, and the mucous membrane showed a low grade inflammation.

The skull was extremely large and the vault thin. The sutures were open, and there was an advanced degree of convolutional atrophy of the inner table.

The convolutions of the brain were markedly flattened, particularly over the dorsolateral surface of the right parietal and occipital lobes, where the cortical markings were indistinct. The cortex in this region had a gelatinous appearance. Beneath the cortex could be palpated an irregular indurated mass. The brain was sectioned horizontally through the basal ganglions and the internal capsule. In the parieto-occipital centrum was a large, irregular, firm, sharply circumscribed mass which extended almost to the surface of the brain. On cross section it measured 6 by 7.5 cm. in its greatest diameters. Near the center of the mass was a hard,

irregular, yellowish white calcareous mass (fig. 2). Sections were taken from this and from adjacent areas for microscopic study.

A section from the central calcareous portion of the tuberculoma disclosed an irregular shell of calcification composed of a fusion of many small crystals. The interior of the shell was structureless. This calcareous formation was surrounded by a fibrous connective tissue scar which had undergone almost complete hyalinization. In the adjacent cerebral tissue the blood vessels had become calcified, the tissue being studded with a large number of round or oval darkly stained granules. The nerve cells in the region were also "calcified,"<sup>22</sup> the encrusted cells still retaining to a great extent their original form.

Sections from the peripheral portion of the tuberculoma showed the typical characteristics of such a lesion: lymphocytes, plasma cells, fibroblasts and giant cells.

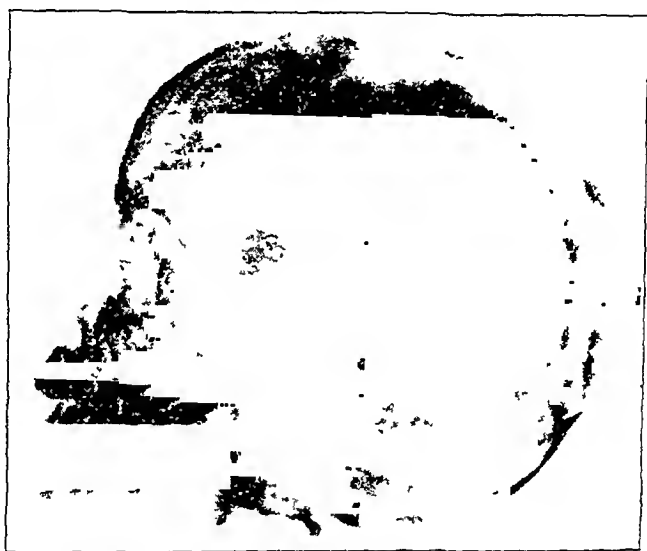


Fig. 1 (case 1).—Roentgenogram of the skull, showing the calcareous mass in the right parietal region. The thinned cranial vault with increased convolutional markings, separation of the suture lines and erosion of the dorsum sellae are all indicative of long-continued increased intracranial pressure.

*Comment.*—This case presents a number of unusual features. The long, continuous course suggests the progressive growth of the tuberculoma. This is further suggested by the characteristic structure of the peripheral portion of the tuberculoma. One might predicate another possibility, however: that a recurrence of activity had occurred in the peripheral portion of the tuberculoma after its central portion had

22. The incrustation of nerve cells with salts which stain deep blue in routine preparation of sections has long been designated as "calcification." These cells are actually covered with a deposit of iron salts, which can be demonstrated by the prussian blue method. The test is imperfect when used in tissues fixed by immersion in formaldehyde for long periods, as was the case in this specimen

become quiescent. The calcification of the blood vessels in the adjacent cerebral tissue is of interest; it represents still another type of process.

This case is important, as it enabled us to determine the characteristics of the process of calcification in a tuberculoma in which there was no question as to the nature of the basic lesion. In so many of the reported cases in which the degenerative changes have completely effaced the typical structure, the question has arisen as to whether one was actually dealing with a tuberculoma. This case serves, then, as a yardstick for further studies.



Fig. 2 (case 1).—Horizontal section of the brain, showing the large tuberculoma (T) in the white matter of the right parietal lobe. The associated calcareous mass (c) appears as an irregular white area lateral to the main part of the tumor. Extensive necrosis of the surrounding brain tissue is evident.

CASE 2.—Symptoms of acute meningeal irritation in a 3 year old boy; opalescent spinal fluid with formation of pellicle; clinical diagnosis, tuberculous meningitis; recovery; progressive osteomyelitis of left metatarsal bones thought to be tuberculous in origin; persistent drainage from stump of amputation, chronic lesion of rib and mastoid wound; downward course and death eight years after onset, with symptoms of pulmonary disease; autopsy: internal hydrocephalus; calcified tuberculoma beneath right cingulate gyrus; noncalcified tuberculoma in left cerebellar hemisphere.

A Mexican boy 3 years of age was admitted to the Los Angeles County Hospital in February 1926 with a story of suddenly becoming ill two weeks previously, after exposure to dampness. Pains in the legs and back were followed by generalized convulsions and vomiting of four days' duration. The child had lost his appetite.

On examination, a bilateral internal squint was noted, associated with retraction of the head and bilateral Brudzinski and Kernig signs. Lumbar puncture disclosed opalescent spinal fluid in which a pellicle promptly formed. The fluid was not under increased pressure. There were 525 cells per cubic millimeter, the type of which was not stated. A roentgenogram of the chest was reported as showing no evidence of tuberculosis. The boy was discharged on March 1 with a diagnosis of tuberculous meningitis.

The child was next seen in the clinic on June 17, 1930, with a deformity of the right foot (equinovarus) thought to have resulted from infantile paralysis, which he had contracted three years before. There were two draining ulcers on the dorsum of this foot.

The boy subsequently contracted osteomyelitis of the metatarsal bones of the left foot. *Because of its character the lesion was suspected of having a tuberculous origin, although no acid-fast organisms were ever found in the exudate.* The left leg was finally amputated in its middle third. The bony lesion proved to be of a tuberculous nature.

A roentgenogram was taken of the chest on July 25, 1931, when the child was brought to the clinic with a chronic papular eruption of the skin. No evidence of pulmonary tuberculosis could be made out.

On Jan. 1, 1932, the boy was readmitted to the hospital with a swelling of two weeks' duration in the right thoracic wall over the seventh rib in the anterior axillary line. A roentgenogram showed alterations in the rib suggestive of osteomyelitis secondary to an abscess in the soft tissues. Resection of the rib was done. Some exudate from the lesion was injected into a guinea pig; subsequently typical tubercles developed in the animal and characteristic acid-fast organisms were recovered. The child was ultimately referred to the Children's Hospital. There was persistent drainage from the recent operative wound, from the stump of the left leg and from sinuses in the region of the sacro-iliac joints.

In October 1933 otitis media on the left developed; this was complicated by mastoiditis followed by generalized convulsions with lateralizing manifestations on the right side. Mastoidectomy was done at the Children's Hospital on October 26.

On March 19, 1934, the boy was readmitted to the County Hospital with a low grade fever and advanced emaciation. There was drainage from the left mastoid wound as well as from the other sites just mentioned. The right knee was swollen and tender. The breath sounds were harsh throughout the chest and were associated with occasional crackling rales at the base of the right lung. The patient died on October 14, at the age of 10½ years, seven years after the onset of his illness.

An autopsy was performed three hours after death by Dr. Eugene Joergensen. Draining sinuses were present in the left mastoid region, in the medial aspect of the supracondylar region of the right arm, in the right anterior axillary line over the seventh and eighth ribs, in the right anterior superior iliac spine, in the lateral aspect of the right knee and in the stump of the left leg.

There were no areas of ulceration or caseation in the lungs. The tracheo-bronchial glands were enlarged and showed considerable caseation. Exploration of the various draining sinuses showed them to be extensive and complicated and associated with the formation of large abscesses.

A circumscribed caseated area about 2 cm. in diameter was observed in the right parietal bone. The inner table of the skull showed advanced convolitional atrophy. The entire central part of the petrous portion of the left temporal bone was the seat of inflammation. The bone had been eroded through to the dura in several places, although the dura itself had not been penetrated.

The convolutions over the dorsolateral surface of the cerebral hemispheres were moderately flattened. The arachnoid in the region of the basilar cisterns was somewhat opaque, and there seemed to be adhesion of this membrane to the pia in the vicinity of the foramina of Magendie and Luschka. The resulting obstruction evidently accounted for the advanced internal hydrocephalus.

Situated at about the middle of the basilar surface of the left cerebellar hemisphere was a firm nodule about the size of a marble, which proved on section to be a noncalcified tuberculoma.

Section of the brain disclosed marked dilatation of the entire ventricular system and thickening of the ependyma. The septum pellucidum was fenestrated, with irregular openings which permitted direct communication between the lateral ventricles. The interventricular foramina and the cerebral aqueduct were markedly dilated, and the anterior wall and floor of the third ventricle were as thin as tissue paper.

In the subcortical white matter of the medial aspect of the right frontal lobe was an irregular, calcified tumor, the longest diameter of which lay in an antero-posterior direction (3 cm.). Its greatest cross-sectional diameters were 1.3 by 0.7 cm. The nodular mass, which presented a peculiar grayish, semitranslucent appearance, was sharply delineated from the surrounding nerve tissue (fig. 3).

Section through the nodule in the right frontal lobe disclosed an irregular calcareous shell embedded in a hyalinized connective tissue scar. The periphery of the shell was composed of a fusion of many small individual crystals of calcareous salts. No definite evidence of tuberculous granulation tissue remained, except for scattered lymphocytes at the margin of the connective tissue capsule. The surrounding brain tissue showed only a loose glial scar.

Section through the cerebellar tuberculoma revealed the characteristic features of such a lesion.

*Comment.*—The pains in the extremities and the vomiting which occurred seven years before death were suggestive of meningeal inflammation, and it is likely that the cerebral invasion took place at this time. Hydrocephalus was probably the result of meningeal inflammation and adhesion about the basilar foramina. If the cerebral and the cerebellar tubercle formed at the same time, one may well wonder why one became calcified and the other did not. The histologic features of the cerebellar lesion were characteristic of a tuberculoma, while those of the frontal lesion were not.

*CASE 3.*—*Epigastric distress, irritability and listlessness in a Mexican boy of 6 years; signs of meningeal irritation; pleocytosis and globulin in spinal fluid; death; tuberculous meningitis; softening of the right corpus striatum with calcified and ossified tuberculoma in external capsule; multiple miliary calcified and ossified nodules in cerebral cortex.*

A Mexican boy aged 6 years was admitted to the Los Angeles County Hospital on July 11, 1935. For three weeks there had been intermittent pain in the upper part of the abdomen with progressive irritability, listlessness and disturbance of

sleep. The past history was essentially negative except for uncomplicated chicken-pox two months before admission. A left internal squint had been present since birth. There was no known contact with tuberculosis.

The child was lethargic and appeared to be chronically ill. The skin over the trunk and extremities was dry and scaly. The pupils were regular and equal and reacted sluggishly to light. An old perforation was observed in the left tympanum; the right was perforated with numerous minute openings. The cervical glands were slightly enlarged. The neck was moderately stiff. Impaired resonance over the upper anterior part of the left lung was associated with bronchial breathing. The deep reflexes showed no irregularities. Kernig and Brudzinski signs were elicited.

Lumbar puncture disclosed a clear, colorless fluid under more than 400 mm. of pressure. There were approximately 100 cells per cubic millimeter, consisting of



Fig. 3 (case 2).—Small calcified tuberculoma in the subcortical white matter of the right frontal lobe. The dilated lateral ventricle was the result of chronic thickening of the arachnoid with adhesions to the pia in the cisterna magna and in the cisterna pontis lateralis.

both lymphocytes and polymorphonuclears, the proportions not being stated. Repeated punctures done almost daily disclosed a clear fluid consistently under high pressure and containing between 70 and 80 cells per cubic millimeter, predominantly lymphocytes. It required from 22 to 24 drops of spinal fluid to reduce Benedict's solution. Quantitatively, the sugar varied between 30 and 40 mg. and the chlorides between 610 and 680 mg. per hundred cubic centimeters. Levison's test constantly gave negative results. Wassermann and Kahn tests were negative. There were 16,000 white cells per cubic millimeter of blood, with 92 per cent polymorphonuclears.

A roentgenogram of the chest showed increased density throughout the left hilar and perihilar regions.

Death came on July 19.

An autopsy was performed fourteen and one-half hours post mortem by Dr. P. C. Humphreys. There was no evidence of pulmonary tuberculosis, and while the tracheobronchial lymph nodes were enlarged and darkened, no actual caseation was noticed. An incidental congenital stenosis of the right ureter with consequent hydronephrosis of the right kidney was discovered.

The convolutions of the brain were generally flattened, particularly those of the dorsolateral surface of the right frontal lobe, which seemed larger than its fellow. About the branches of the middle cerebral vessels were seen characteristic miliary nodules. In the basilar cisterns the exudate was so abundant as to obscure the regional structures. On the basilar surface of the right frontal lobe, adjacent to the gyrus rectus, was an irregular area of discoloration and softening.

On coronal section the cerebral tissue was seen to be hyperemic. The lateral ventricles were markedly dilated, the anterior horns showing a deflection toward the left with narrowing on the right. In the genu of the corpus callosum was a small tuberculoma. Section through the softened area on the basilar surface of the right frontal lobe showed the softening to extend into the basal ganglions and external capsule on this side. In the midst of this softened area, in the external capsule, was a small circumscribed calcareous mass, the structure of which suggested a calcified tuberculoma (fig. 4). This mass was situated at a point opposite the outer posterior part of the putamen. On closer study the mass was seen to be made up of several distinct areas of calcification. It measured 1 by 0.5 cm. in its greatest diameters.

Further sections of the brain showed a number of other small calcified nodules, two in the cortex of the left parietal lobe and two in that of the left frontal lobe. The nodules varied from 2 to 6 mm. in diameter. As in the case of the first mass, they were made up of two or three separate masses which had become fused.

Microscopically, the typical characteristics of tuberculous meningitis were in evidence. Sections through the various calcareous masses disclosed an irregular calcified shell enclosed within a hyalinized connective tissue capsule, which corresponded closely in structure to that observed in the 2 cases just cited. In addition, osteoid tissue in the process of formation was noted in portions of this shell. Apparently, either the irregular calcareous masses were deposited within this osteoid tissue or the osteoid tissue had developed around the deposits. The new-formed bone was not evenly calcified, as is normal bone.

In the hyalinized scar elongated, smooth-margined slits suggested the recent presence of cholesterol crystals.

The only possible evidence of an inflammatory process was the presence of thinly scattered lymphocytes at the margin of the connective tissue capsule.

The small blood vessels in the nerve tissue at the margin of the mass were the seat of irregular, laminated calcospherites.

*Comment.*—This case is of special interest because, as in case 2, there were in the brain both calcified and noncalcified lesions. Again the question arises: Are these lesions of the same age? If so, why did one type of lesion undergo calcification and ossification while the other did not? We have found no answer to this question.

Perhaps of even greater interest is the occurrence of actual bony formation in the large tumor as well as in the miliary nodules. This adds another instance to the list of intracranial lesions in which formation of bone may take place.



THE SIGNIFICANCE OF CALCIFICATION AND OSSIFICATION IN  
TUBERCULOMA OF THE BRAIN

Deposition of calcium salts and, less commonly, formation of true bone are consequences of healing in tubercles, regardless of their location. These processes occur typically in the lymph nodes along the respiratory passages and in tubercles of the lung. Because of the more

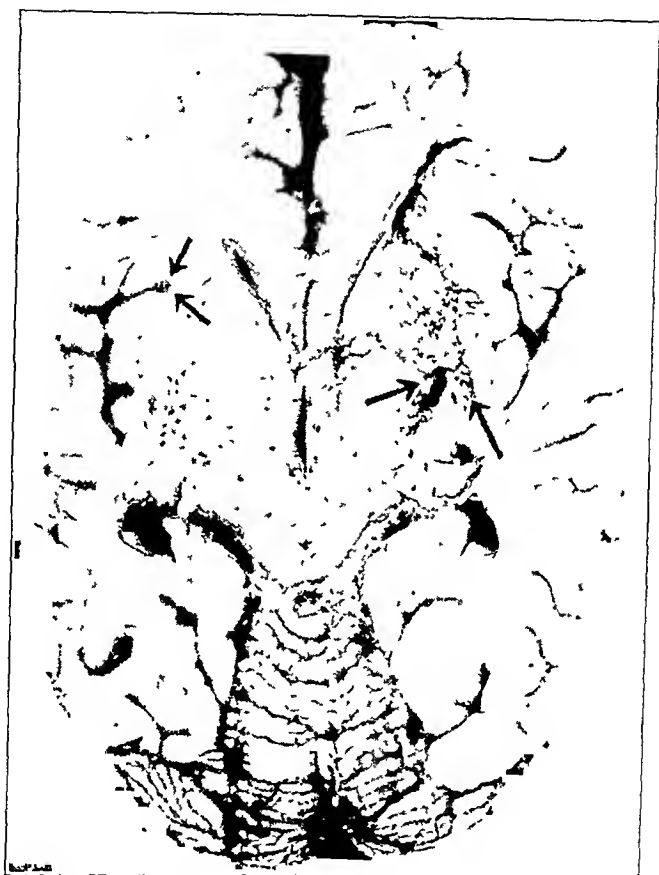


Fig. 4 (case 3).—Horizontal section of the brain, showing extensive softening of the right basal ganglia and centrum of the right frontal lobe and external capsule. A small calcified tuberculoma was observed (arrows) in this area. On the left side were seen several small calcified and ossified tubercles (arrows) in the leptomeninges

malignant character of tuberculous inflammation in the meninges and brain, healing of tubercles in these structures is much less common, and calcification and ossification would therefore be observed less frequently. As has been repeatedly emphasized, healing of a tubercle in the brain or elsewhere is not absolute evidence of complete quiescence "Healed"

tubercles in the meninges<sup>23</sup> or calcified tuberculomas within the brain tissue may be the source of fatal tuberculous meningitis.

As has been shown in the foregoing discussion of cases previously reported and of those which we personally studied, regressive changes in tuberculomas of the brain may be followed by deposit of calcium or by formation of bone. To be sure, the distinction between the two processes has not always been clearly drawn, particularly in the earlier reports, in which critical histologic studies were not always made. It is obvious that calcification is more common than ossification and probably precedes it. In Siemon's case ossification as well as calcification was observed in a tuberculoma of the frontal lobe. In one of our cases (case 3) the same condition was seen in multiple tuberculomas of the cerebral hemispheres.

#### CHARACTERISTICS OF CALCIFICATION AND FORMATION OF BONE

The deposit of calcium as a consequence of a tuberculoma may occur in any one of several situations. It may be noted in the walls of blood vessels of the brain at the margin of a tuberculoma. It may similarly be observed in the walls of vessels in the central portion of a partially degenerated tuberculoma. More commonly it occurs in the form of a shell within the necrotic center of a tuberculoma.

Calcification in the walls of blood vessels at the margin of a tuberculoma is not characteristic of this lesion. It has been observed at the margins of gliomas and even of the more malignant glioblastomas.<sup>24</sup> Calcareous salts are deposited in the form of isolated round or oval globules, which tend to coalesce and to outline the blood vessels in the neural tissues (fig. 5). The process is believed to be due to a local disturbance of tissue respiration. The soluble calcium salts are thought to unite with an excess of carbon dioxide to form the insoluble calcium carbonate which is deposited in the walls of the smaller blood vessels.

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23. The matter of a cure in cases of tuberculous meningitis has always been a subject of much interest. That healing can occur in each case has been proved beyond a doubt, as has been indicated by the studies of A. E. Martin (*The Occurrence of Remissions and Recovery in Tuberculous Meningitis*, *Brain* **32**:209, 1909) and A. Cramer and K. Bickel (*La méningite tuberculeuse est-elle curable?* *Ann. de méd.* **12**:226, 1922). As far as we can learn, there have been no reported cases of calcification in healed meningeal tubercles. In one of the cases reported here (case 3) and in another case of healed tuberculous meningitis, to be reported elsewhere (Courville, C. B., and Evans, H. S.: *Residual Lesions in Healed Tuberculous Meningitis*, *Bull. Los Angeles Neurol. Soc.* **2**:125, 1937), calcified and ossified meningeal tubercles were discovered at autopsy.

24. Courville, C. B., and Adelstein, L. J.: *Intracranial Calcification with Particular Reference to That Occurring in the Gliomas*, *Arch. Surg.* **21**:801 (Nov.) 1930.

The second type of calcification is similar to the one just described, in that calcium is deposited in blood vessels within the tuberculoma (fig. 6). The vessels are quite clearly shown in the histologic preparation, which suggests that complete necrosis has not taken place. The presence of the calcium is probably to be accounted for in a similar way.

In the third type, which is the common and characteristic one, calcification follows more marked regressive changes in the lesion. In fact, identifying remains of the tuberculoma are usually not observed, and it has often been difficult or impossible to identify the lesion. We

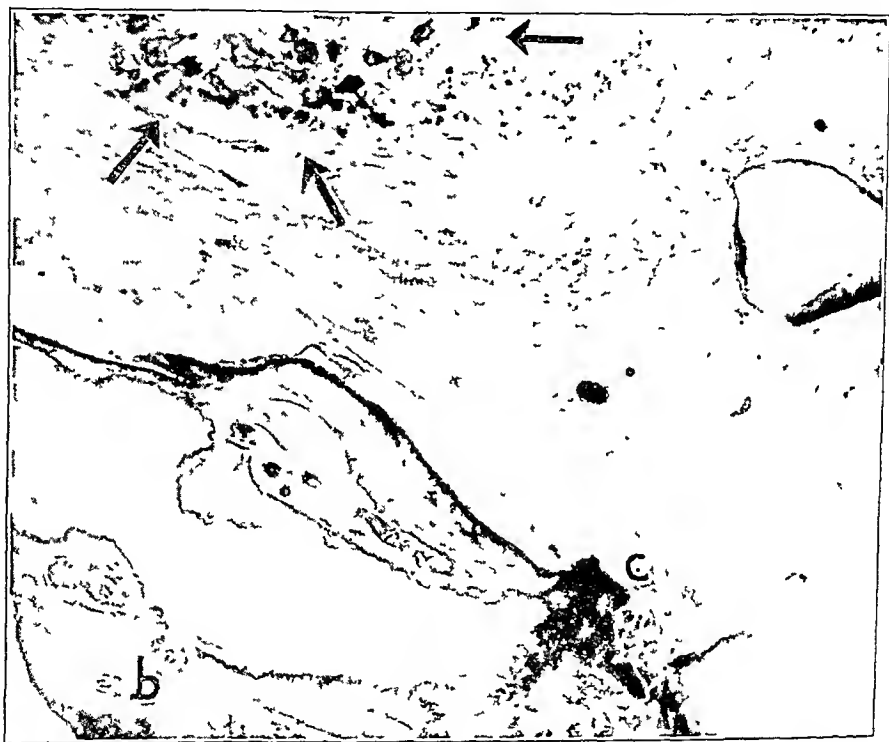


Fig. 5 (case 3) —Calcification of blood vessels (arrows) in the brain tissue at the margin of the tuberculoma, in which both calcification (*c*) and formation of bone (*b*) have occurred. Hematoxylin and eosin stain;  $\times 45$

shall show, however, that the process of calcification and ossification is characteristic of the lesion and that one can be assured of the original nature of the lesion on this basis. In our cases this conclusion is made certain, for in case 1 calcification occurred only in the central portion of an unusually large tuberculoma, and in cases 2 and 3 the association of calcified and typical noncalcified lesions made the situation obvious.

The lesion consists of three well defined zones or areas: (1) an outer zone of hyalinized connective tissue, (2) a more or less irregular calcareous shell and (3) a structureless necrotic core. The outer layer

or zone of hyalinized connective tissue may contain some residual cellular elements indicative of a tubercle (round cells, plasma cells, fibroblasts and new-formed blood vessels), but these are often entirely absent. This layer, which has been designated by other writers as the capsule, is usually sharply delineated from the enveloping neural tissue. The zone is not of uniform width. Owing to the collapse and fragmentation of the calcareous shell, it may be wide in some regions and narrow in others.

The calcareous shell, which in this connection is of particular interest, is composed of myriads of small calcospherites which become confluent

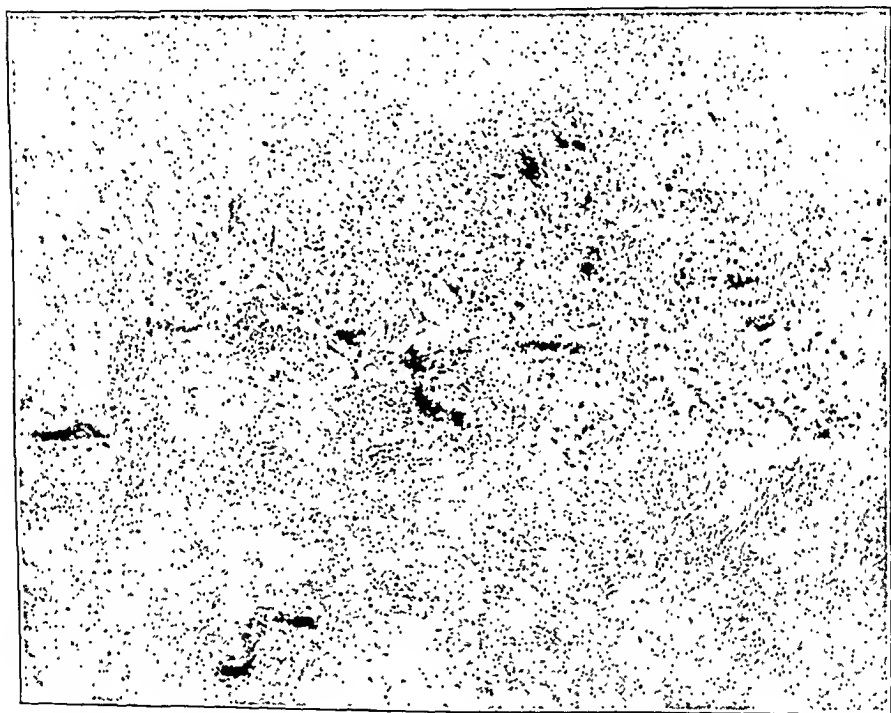


Fig. 6 (case 1).—Calcareous salts deposited in blood vessels in an incompletely necrotized portion of the large cerebral tuberculoma. This process occurred a short distance from the heavily calcified shell shown in figure 7. Hematoxylin and eosin stain;  $\times 95$ .

to form a band, often of considerable width (fig. 7). These individual globules, seen best in the looser outer portion of the zone, are small, discrete, round or slightly oval masses with a dark periphery and a lighter center. The shell is usually collapsed and fragmented, not forming a perfect or complete sphere. It is likewise not of uniform thickness.

The central, structureless core probably represents the remains of the central, necrotic portion of the tubercle. It is made up of small pale granules. The gradual absorption of this material, with contraction of

the connective tissue capsule, probably explains the collapse and fracture of the calcareous shell.

It is of importance in this connection to learn whether calcification in tubercles is identical regardless of the type of tissue in which the lesion is situated. A survey of the literature on the characteristics of calcification in tuberculomas has largely been fruitless. Scattered remarks in textbooks indicate the calcification to be central,<sup>25</sup> as is the case in experimental tubercles.<sup>26</sup> Actual study of a calcified tubercle in a

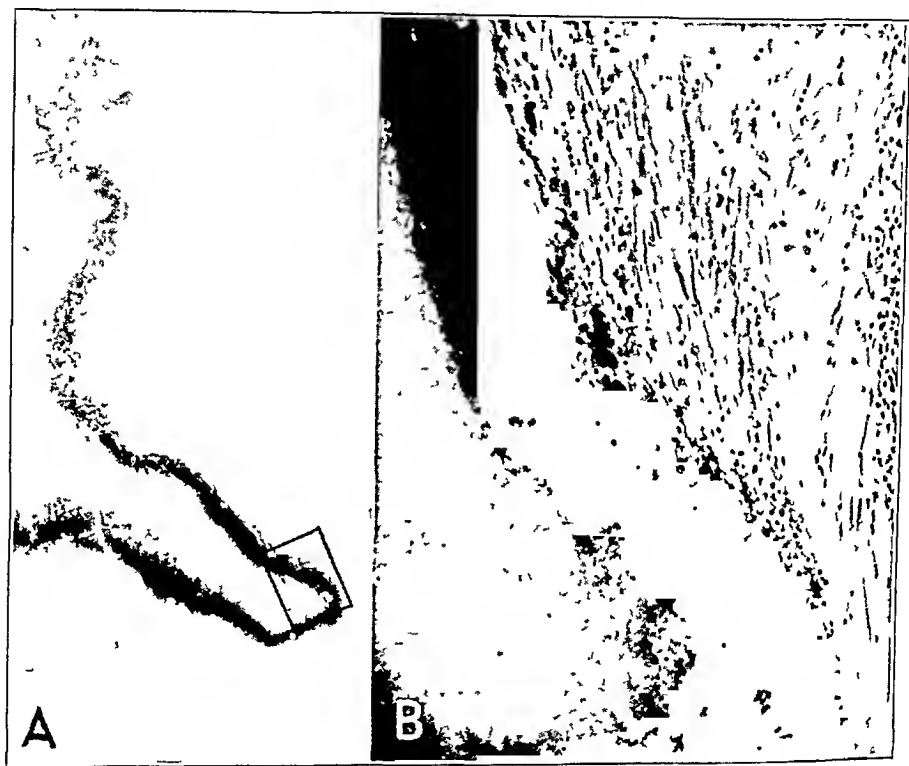


Fig. 7 (case 1)—Calcareous shell in tuberculoma of the brain. *A* shows a portion of the irregular, contracted shell with a structureless, necrotic center,  $\times 30$ . *B* shows an enlarged portion of the shell, which is composed of myriads of crystals of calcium salts;  $\times 145$ . Hematoxylin and eosin stain

mediastinal lymph node showed a calcareous shell, although the central core was small. This suggests that the process is essentially the same,

25. Delafield, F., and Prudden, T. M. *A Text-Book of Pathology*, ed 15, revised by Frances Carter Wood, Baltimore, William Wood & Company, 1931, p. 717.

26. Spies, T. D. The Calcification of Tubercles by Means of Irradiated Ergosterol, *Am. J. Path.* 6:337, 1930; The Calcification of Tubercles by Means of Irradiated Ergosterol in Experimental Chronic Tuberculosis, *Am. Rev. Tuberc.* 23:169, 1931.

although the central core may be greater or less in extent, depending somewhat on the type of tissue in which the tubercle is located (or on the blood supply of the tissue).

Formation of bone is a less common and probably a secondary process. In some lesions new-formed bone is observed in some portions of the calcarous shell. It has never been known to form a complete bony shell, although theoretically such an eventuality is possible. In some cases the bone assumes the appearance of the adult type by deposit of calcium in the osteoid tissue.

#### POSSIBLE MECHANISM OF CALCIFICATION AND OSSIFICATION

The possible reasons for the deposit of calcium in these healed tuberculomas merit consideration. It has been found that calcium tends to be deposited in lesions containing or composed of completely dead tissue which for any reason is not absorbed.<sup>27</sup> A long-existent tuberculoma in any location presents a classic example of such a situation. The extensive central necrosis or caseation represents tissue which is completely dead and which, because of the poor circulation, is not absorbed. Just what intimate situations exist which favor the deposit of calcium salts is not entirely clear, but it is likely that there is precipitation of calcarous salts in the exterior portion of the tubercle, where the circulation is still not entirely obliterated. The impaired tissue respiration probably favors the union of carbon dioxide and the soluble calcium salts in the blood to form insoluble calcium carbonate.

The occurrence of calcium in tubercles has also been explained on the theory that fatty acids attract calcium and, by combining with it, form calcium soaps, which unite with soluble phosphates and carbonates to form insoluble calcium phosphates and carbonates.<sup>28</sup>

Still another factor should be considered. In healed tuberculomas there is gradual replacement of the necrosed tissue by connective tissue, which contracts to form a fibrous scar. This is strongly suggested by the presence of connective tissue, which forms the remainder of these healed lesions. This connective tissue evidently undergoes more or less complete hyalinization, as is again suggested by the absence of structure in the scar immediately about the calcarous mass. This process of hyalinization is also said to favor the deposit of calcium. Whether the calcium is actually deposited in the necrotic tissue near the periphery of a tubercle or whether replacement with connective tissue and hyalinization precede the process is not evident.

27. Wells, H. G.: *Chemical Pathology*, ed. 5, Philadelphia, W. B. Saunders Company, 1925, p. 489.

28. Karsner, H.: *Human Pathology*, ed. 3, Philadelphia, J. B. Lippincott Company, 1931, p. 96.

From this purely morphologic study, the relative importance of these three factors—impaired tissue respiration, formation of fatty acids and hyalinization of connective tissue—in the process of calcification cannot be determined. One can only state that the process begins in a zone just within the external margin of the tuberculoma, probably at the juncture of the central necrotic area and the peripheral border of granulation tissue. Thus is formed a calcareous shell, which ultimately becomes irregular and broken as the connective tissue at the border contracts and the necrotic material in the center is slowly absorbed.

This explanation, however, does not suffice for the occasional calcification of small vessels in the central necrotic regions. In such cases necrosis with occlusion of blood vessels is apparently not complete, and the theory of disturbed tissue respiration would apply more particularly.

The formation of bone within a tuberculoma is evidently much less common, if the facts gathered from a survey of the literature and from our own experience are of any significance. For example, we found in the report of Siemon the only definite statement that bony formation was present in a tuberculoma. It occurred in a tuberculoma in but 1 of our cases, but in this case it occurred also in a number of miliary tubercles which had also undergone the process of calcification. The bone which is present is characteristic of new-formed osteoid tissue in which calcium has not yet been deposited (fig. 8). A study of the details in our case is of interest. Either the bone developed within the area in which calcium had been deposited, or calcium was laid down in the new-formed bone in the same way as it was in the hyalinized connective tissue, namely, in the form of conglomerations of calcareous crystals (fig. 9). The appearance of the lesions lends strength to the conception of Nicholson<sup>29</sup> that the presence of calcareous salts in an abnormal situation tends to stimulate the connective tissue cells in this region to undergo a metaplasia into bone cells.<sup>30</sup>

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29. Nicholson, G. W.: *The Formation of Bone in a Calcified Epithelioma of the Skin*, *J. Path. & Bact.* **21**:287, 1916-1917.

30. This brings up the interesting problem as to the actual mechanism of bone formation in abnormal situations. Our observation again seems to bear out the theory of R. Leriche and A. Policard (*The Normal and Pathological Physiology of Bone*, St. Louis, C. V. Mosby Company, 1928) that bony formation is not the secretory product of a specific cell but is rather the result of a transformation of connective tissue cells to osteoblasts and that the resulting osteoid tissue is transformed into true bone by a subsequent deposit of calcium. This is evidently an entirely different process than that occurring, for example, in a case of metastatic osteogenic sarcoma of the brain, in which formation of bone was evidence of a specific cellular tendency to perform this function (Harding, W. G., and Courville, C. B.: *Bone Formation in Metastases of Osteogenic Sarcoma* Report of Case with Metastases to the Brain, *Am. J. Cancer* **21**:787, 1934)

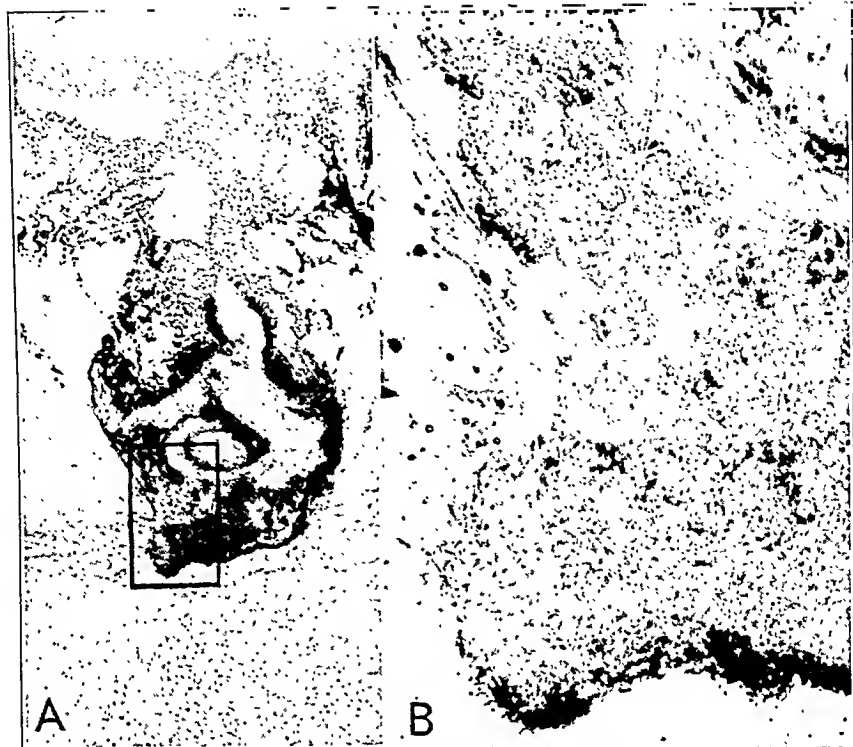


Fig. 8 (case 2).—Osteoid tissue forming in a calcareous shell in a small tuberculoma of the brain. *A* shows a portion of the calcareous shell;  $\times 30$ . *B*, enlargement, shows newly-formed osteoid tissue in the calcareous shell;  $\times 160$ . Hematoxylin and eosin stain.

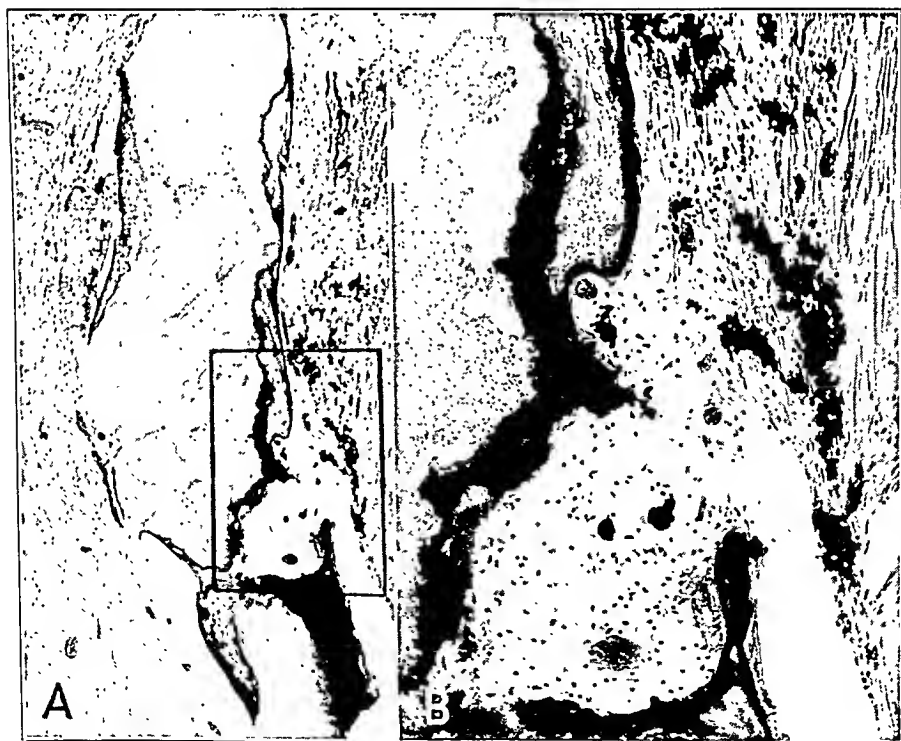


Fig. 9 (case 3).—Capsule enclosing a calcareous and osseous shell of a cerebral tuberculoma. *A* shows the collapsed shell with its necrotic center; slightly reduced from  $\times 45$ . *B* shows a portion of the capsule with deposits of calcareous salts and bony formation in the adjacent shell; slightly reduced from  $\times 135$ . Hematoxylin and eosin stain.



Formation of bone seems to take place deep within the calcareous shell, where in turn an irregular and usually incomplete bony shell may occur. At times only small areas of the shell may become ossified (fig. 10).

From our observations one would conclude that the formation of new bone is a later process, occurring some time after calcium has been deposited. In fact, it is probably encouraged by the presence of calcareous salts, which tend to stimulate the metaplasia of connective tissue cells into osteoblasts. The reported cases are too few and the details



Fig. 10 (case 3).—Formation of bone in a conglomerate meningeal tubercle. *A* shows two separate calcareous shells with capsules, the larger of which has collapsed. Calcium has also been deposited in the regional blood vessels (arrows);  $\times 24$ . *B* shows the detail of the bony formation, which is assuming adult type with deposit of calcium. Calcareous salts in the shell (upper right) and in the capsule (right) are also shown;  $\times 96$ . Hematoxylin and eosin stain.

too obscure for one to draw any conclusions as to the length of time required for this process.

#### SUMMARY AND CONCLUSIONS

1. The occurrence of calcification or ossification in tubercles of the brain, evidently indicative of partial or complete healing of these lesions.

is relatively rare. We have collected a series of 15 cases from the literature and have added 3 which came under our observation.

2. Calcification or ossification occurs in about 7 per cent of the cases of tuberculoma of the brain.

3. The process of calcification or ossification may occur in miliary meningeal tubercles ("healed tuberculous meningitis") as well as in gross tuberculomas. It does not necessarily occur in all tubercles or tuberculomas present in the brain in a given case.

4. The process of calcification is preceded or accompanied by a transformation of the peripheral zone of granulation tissue into a zone of connective tissue, which becomes more or less completely hyalinized, presumably owing to impairment of its circulation incident to its contraction.

5. Calcium is deposited in the periphery of the central necrotic area and beneath the connective tissue capsule to form a calcareous shell. Whether calcium is deposited in the dead tissue before or after fibrosis and hyalinization occur is unknown, since the intermediate stages have not as yet been studied. The shell assumes an irregular contour and is often broken, probably as a result of contracture of the connective tissue capsule and gradual absorption of the underlying necrotic material. We believe that this irregular, broken calcareous shell is characteristic of the deposit of calcium in tubercles and that it does not occur in any other intracranial lesion with which we are familiar.

6. The actual mechanism of calcium deposition is uncertain. It may be the result of impaired tissue respiration, it may be due to the presence of fatty acids in the decadent tissues, or it may possibly be favored by hyalinization of the adjacent connective tissue capsule. Since it is deposited in the form of a shell beneath the external connective tissue layer, accessibility to the circulation seems to be necessary, possibly because the blood is the source of calcium.

7. The process of formation of bone is less common, and in the 2 cases available for study (case of Siemon and our case 3) in which this occurred calcification as well as bony formation was present. This suggests that the presence of calcium favors formation of bone, according to the conception of Nicholson. Possibly some unknown stimulating effect of the calcium on the connective tissue favors metaplasia of connective tissue cells into osteoblasts.

# CALCIFICATION ABOUT THE FLEXOR CARPI ULNARIS TENDON

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During the past year or so we have had an opportunity of studying a number of patients, all of whom presented such strikingly similar symptoms as to warrant their being grouped together as having a definite clinical entity. Typically, there were sharply localized pain and tenderness over the area around the pisiform bone; a pathognomonic limitation of motion at the wrist; occasional signs suggesting an inflammatory reaction; a characteristic roentgenogram, and early subsidence of symptoms. When we referred to the literature for some help in understanding the condition, we were afforded scant assistance. Except for a single case reported by Cohen<sup>1</sup> and the casual statement of Codman<sup>2</sup> that he knew "of one case in the flexor carpi ulnaris," no mention could be found of the condition, either in the clinical or in the roentgenologic literature. Neither Codman nor Cohen presented any histologic evidence to justify their belief that the site of the lesion was the tendon itself. We are inclined to share the opinion of Codman and Cohen, but we can offer no positive proof and the present consideration is undertaken from clinical rather than from pathologic interest.

Though all of our cases showed a basic similarity, there seemed to be sufficient variation to justify subdivision of the conditions into three main types similar to those suggested for injuries to the supraspinatus tendon: (1) a hyperacute form, (2) an acute form with calcification and (3) an acute form without calcification.

## THE HYPERACUTE FORM

### REPORT OF CASE

CASE 1.—H. H. G., a 29 year old man, was admitted to the hospital on Dec. 9, 1935, complaining that two days before he had noted a dull pain in the left wrist while making a plaster of paris splint. During the day the pain became more

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From the service of Dr. Harry Finkelstein at the Hospital for Joint Diseases.

1. Cohen, I.: *Am. J. Surg.* **38**:172, 1924.

2. Codman, E. A.: *Boston M. & S. J.* **154**:613, 1906; *The Shoulder, Boston.*

The Author, 1934, pp. 68-83.

severe, and all motion of the wrist became so painful and so restricted that an anterior splint was applied to immobilize the wrist. Despite this rest and the exhibition of large amounts of salicylates, sleep was impossible because of the throbbing pain on the ulnar side of the volar aspect of the left wrist. Early the following evening the patient had a mild chill and a feeling of malaise and anorexia. The temperature was 102 F. The hand and wrist were held in neutral position and there was an area of redness and swelling directly over the left pisiform bone. Extending upward as far as the middle of the upper arm, there were several red streaks, suggesting lymphangitis. There was marked tenderness over the swollen area, but no evidence of fluctuation. Any attempt at normal



Fig. 1 (case 1).—Anteroposterior view, showing an irregular, snowshoe-like shadow of varying density over the upper end of the pisiform bone. On a later roentgenogram this shadow assumed a more sausage-like shape, and still later it disappeared completely.

extension or radial deviation of the wrist caused exquisite pain in the swollen area. There was no evidence of motor or sensory disturbance in the hand and no enlargement of the epitrochlear or axillary glands. The symptoms did not subside, and the patient was sent to the hospital, where the clinical findings were essentially the same. The temperature remained at about 100 F.; the pulse rate was somewhat over 100 and the impression was obtained that the patient was suffering from lymphangitis.

A roentgenogram (fig. 1) made after his admission to the hospital revealed several irregular densities in the soft tissues, on the inner aspect of the wrist and between the styloid process of the ulna and the pisiform bone. These densities suggested osteitis of an accessory bony nucleus, or osteochondritis of the pisiform

bone. The swollen area was aspirated in an effort to determine the presence of pus, but none was obtained.

During the forty-eight hours following his admission to the hospital the patient was given hot hand baths, and the pain gradually subsided. At this time a roentgenogram revealed that there was a distinct diminution in the density of the previously mentioned small body below the ulnar styloid process. Irregular calcification was distributed longitudinally from a point immediately below the styloid process of the ulna, downward into the soft tissues and externally to the pisiform bone, for about 1 inch (2.5 cm.). The neighboring bones showed no specific alteration. Roentgenographically, the appearance was extremely unusual, and not



Fig. 2 (case 2).—The shadow in this case is circular, as if it were enclosed in a limiting membrane, such as a bursa.

characteristic of any pathologic process. The roentgenogram suggested calcification in the ligamentous structures of the part. On the fifth day pain had completely disappeared. A roentgenogram subsequently taken for check-up purposes revealed complete disappearance of any densities, and all irregularities in the wrist had completely disappeared. (An almost identical process subsequently developed at the insertion of the triceps.)

#### THE ACUTE FORM WITH CALCIFICATION

CASE 2.—M. P., a 50 year old woman, was first seen in the outpatient department on Nov. 9, 1936. There was a history of pain, redness and swelling over

the ulnar aspect of the left wrist for about one week. No history of any direct blow or recent acute illness could be elicited. Examination disclosed redness, swelling and pseudofluctuation over the ulnar half of the volar aspect of the left wrist. Extending upward along the ulnar border of the forearm there was a moderate induration. There was marked tenderness on pressure over the pisiform bone, with marked pain on radial or dorsal deviation of the hand. Clinically, the condition resembled acute tenosynovitis or osteomyelitis of the lower end of the ulna. A roentgenogram (fig. 2) revealed a calcific deposit between the styloid process of the ulna and the pisiform bone. The diagnosis was thereupon clarified,



Fig. 3 (case 3).—Lateral view. The shadow in this case is lacelike, suggesting a Medusa head, and seems to arise directly from the periosteum of the pisiform bone.

and the patient's wrist was strapped and physical therapy advised. The patient was given short wave therapy for one or two treatments. On her return to the outpatient department for one follow-up examination, the symptoms had completely subsided. Since that time she has not returned for examination.

CASE 3.—S. G., a 38 year old man, was first seen on Oct. 27, 1936. A cellist by profession, the patient stated that he first noted pain in his left wrist six or eight months before, when he struck the volar aspect of his left wrist against the belly of the cello while advancing into the higher positions. In spite of inter-

mittent pain which occurred only on exertion, the patient received no treatment and continued at his work. Two days before his admission to the hospital the pain suddenly became excruciatingly severe, and the patient was forced to discontinue playing the cello. Examination revealed marked tenderness over the left pisiform bone, directly at the insertion of the flexor carpi ulnaris. There was moderate swelling, but no inflammation and no redness. Dorsal and radial deviation caused extreme pain. A roentgenogram (fig. 3) showed a hazy, serpentine calcification, which suggested periostitis, and a destructive process in the pisiform bone. Experience had, however, taught us to discount this roentgen picture. The

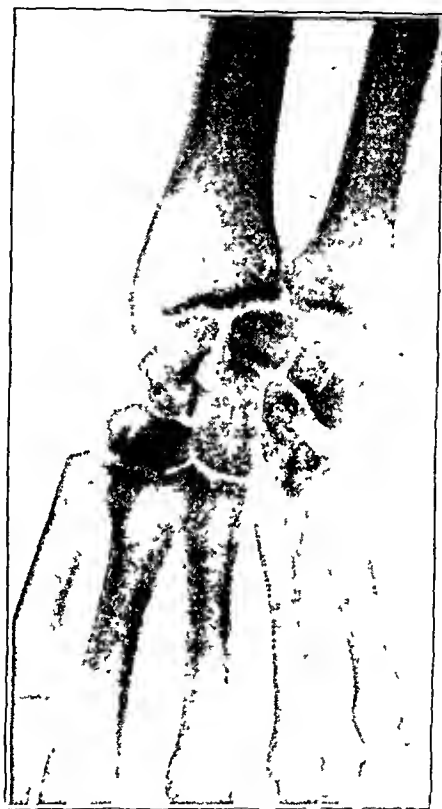


Fig. 4 (case 4).—The irregular, oval shadow is located nearer the tip of the ulna than in the other cases.

patient's hand was strapped, and he was given several applications of short wave therapy and a mild analgesic. Within three days the symptoms had completely disappeared, and the patient was able to resume his usual activities.

CASE 4.—The patient was a private patient of Dr. Harry Sonnenschein, who gave us permission to reproduce the roentgenogram. The details of the case are not available, but it is reported that several months after a fracture of the elbow the patient suddenly began to complain of severe pain in the wrist. A roentgenogram (fig. 4) showed the typical calcification. The wrist was immobilized, and within three or four days the symptoms of pain, swelling and limitation of motion had vanished completely.

## ACUTE FORM WITHOUT CALCIFICATION

CASE 5.—R. G., a 37 year old woman, was first seen in May 1935, with a history of sudden pain over the left pisiform bone. She believed that she might have struck herself while at her housework. No history of recent illness was obtained. Moderate swelling, redness and marked tenderness on pressure over the pisiform bone were noted. There was marked pain on radial and dorsal deviation of the hand.

A roentgenogram taken at this time was reported as being "negative." There was, however, a peculiar triangular shadow in the greater multangular bone, suggesting fracture or embryonal fissure. The wrist was strapped, and the patient was given physical therapy. After several treatments the symptoms completely subsided. In March 1936, after a blow against the lower surface of her right forearm, the patient complained of pain in the right wrist. Examination three days after the alleged injury showed definite swelling over the pisiform bone, with slight redness and elevation of the local temperature. The area was exquisitely tender to the touch. No fluid could be felt in the area. There was marked accentuation of pain on passive extension of the wrist and on active flexion against resistance. The patient was advised to have a roentgenogram taken, but she refused, since the symptoms began to subside immediately after the first short wave treatment. Within several days the symptoms completely disappeared, and the patient has been well ever since.

CASE 6.—P. D., a 38 year old man, was first seen on July 29, 1936, complaining of pain of one week's duration on the volar aspect of the right wrist. There was no history of any definite blow or acute illness. Examination disclosed swelling over the proximal row of carpal bones on the ulnar side of the right forearm. There were no signs of local inflammation. There was marked tenderness on pressure just over the pisiform bone, at the insertion of the flexor carpi ulnaris tendon. The patient was advised to have a roentgenogram taken, but he did not return for a follow-up examination.

The following two cases were observed in the practice of Dr. Daniel Levinthal, of Chicago, who has given us permission to report them.

CASE 7.—F. L., a 40 year old man, an executive, was seen on March 26, 1935. He complained of pain, swelling and limitation of motion of the left wrist of fifteen days' duration. No other joints were involved, and there was no history of injury.

Examination revealed swelling over the volar aspect of the left wrist, with palpable thickening and tenderness of the flexor carpi ulnaris tendon. Extension of the wrist was painful. There was no obvious focal infection, although the tonsils had not been removed and roentgen examination of the teeth had not been made recently.

Roentgenograms failed to reveal any pathologic appearance of the bones, but in the second film the roentgenologist noted fluid in the course of the flexor carpi ulnaris tendon.

Treatment consisted of application of a dorsal splint which maintained the wrist in flexion, and gentle physical therapy. Improvement began promptly and was steady. The patient was last seen on April 9, 1935, at which time he was almost, if not completely, free from symptoms.

CASE 8.—M. M., a 32 year old broker, was seen on Nov. 18, 1936. He complained of pain and swelling of the right wrist of twenty-four hours' duration.



with radiation of the discomfort up the forearm. The onset had been sudden, and there had been no injury. No other joints were involved.

Examination revealed redness, tenderness and swelling along the course of the lower end of the right flexor carpi ulnaris tendon. Pain was elicited on extension, and relief was obtained by flexion of the wrist.

Treatment consisted of application of a dorsal plaster splint, with the wrist in moderate flexion, and gentle radiant heat. The patient was last seen one week later, on Nov. 25, 1936, and he was completely relieved except for slight tenderness, which we later heard disappeared in a short time.

#### COMMENT

Though we have reported a relatively insignificant number of cases, we believe the condition described is more common than has been realized. It is hoped that the future will disclose many additional instances of the disability. Because the affliction has been of such short duration and has responded readily to conservative therapy, we have not felt justified in removing pathologic material. However, we are hopeful that this defect in our presentation may be remedied shortly. In the absence of any pathologic specimen we have been forced to infer the location of the calcium deposition. Anatomically considered, the site of the pathologic process may be: (1) the occasional bursa subadjacent to the flexor carpi ulnaris, (2) the peritendinous soft tissues, (3) the tendon itself. From a clinical point of view, the syndrome here presented resembles in many respects that described for the supraspinatus tendon by Codman, Brickner,<sup>3</sup> Moschcowitz<sup>4</sup> and others. It resembles also a similar condition found in the gluteus medius muscle, which has more recently been described by Goldenberg and Leventhal.<sup>5</sup> Though it is known that in both the supraspinatus and the gluteus medius tendon the biologic process probably consists of calcification and later ossification in an area of necrosis in a tendon, the former condition is still erroneously referred to as subacromial or subdeltoid bursitis, while the latter is described as peritrochanteric bursitis or as calcareous gluteal bursitis. The same possibility for misapprehending the location of the calcification presents itself with the flexor carpi ulnaris tendon as with the other two tendons just mentioned, for an occasional bursa is to be found between the tendon and the volar aspect of the pisiform bone, which forms part of its insertion. This bursa appears to have been first described by Monroe,<sup>6</sup> who stated that there is a very small bursa between the tendon of the flexor carpi ulnaris and the os pisiforme.

3. Brickner, W.: *Am. J. Surg.* 30:108, 1916; *Am. J. M. Sc.* 149:351, 1915.

4. Moschcowitz, E.: *Am. J. M. Sc.* 150:115, 1915.

5. Goldenberg, R. R., and Leventhal, G. S.: *J. Bone & Joint Surg.* 18:205, 1936.

6. Monroe, A.: *Outline of the Anatomy of the Human Body in Its Sound and Diseased State*, Edinburgh, A. Constable & Co., 1813, vol. 1, p. 471.

Other anatomists either have made no mention of the bursa or have dismissed it with passing reference to its occasional presence. Gruber has been cited as having made a special study of this bursa, but his report was not accessible for reference. Apart from the fact that calcification within a bursa does not occur, the size of the bursa as compared with the varying appearance of the shadow in the same person would preclude the belief that the bursa was the site of the deposition of calcium.

On the other hand, the anatomic disposition of the tendon readily explains the variations in the shadow seen in the roentgenograms. Frohse<sup>8</sup> gave an excellent description of the insertion of the flexor carpi ulnaris tendon. He considered the pisiform bone as a sesamoid, situated in the tendon. Before its insertion into the pisiform bone, the tendon gives off two slips: a volar slip, described by Henle,<sup>9</sup> which makes up the ligamentum carpi volare, and a dorsal slip, which winds around to the dorsum and is inserted into the ligamentum carpi dorsalis. After its insertion into the pisiform bone, the tendon is continued downward and medially, as the pisohamate ligament, which terminates in the ligamentum basum volare. It is probable that the shape and size of the calcification depend in large degree on the location and extent of the deposition of calcium in the tendon or the peritendinous tissues.

The possibility that the calcification may be located in the peritendinous tissues has already been noted by Finkelstein.<sup>10</sup> It is well demonstrated in the following case, in which the calcification was seen on the radial side of the volar aspect of the wrist. The details of this case were supplied by our mentor, Prof. Arthur Steindler.

CASE 9.—H. D., a 32 year old white woman, a physician, was first seen Nov. 20, 1936. In April the patient had noted pain on the volar surface of the wrist at the base of the greater multangular bone. She said motion and work made it ache. On immobilization, discomfort subsided. The pain had gradually become worse, and the wrist was tender to pressure. One month previous to the patient's first visit a lump was noted, and of late her wrist had been aching constantly. At times, in the evenings, she noted that her wrist was swollen, causing much discomfort.

On examination a tender lump was noted. The laboratory tests which were performed showed no abnormality. The roentgenogram (fig. 5) showed a small round radio-opacity on the volar aspect of the hand. Some question was raised as to whether this shadow might not represent an accessory ossicle. This opinion

7. Footnote deleted by author.

8. Frohse, Fritz, and Frankel, Max, in von Bardeleben, K.: *Handbuch der Anatomie des Menschen*, Jena, Gustav Fischer, 1908, vol. 2, pt. 2, p. 122.

9. Henle, J.: *Handbuch der systematischen Anatomie des Menschen*, Braunschweig, F. Vieweg u. Sohn, 1871, vol. 1, pt. 3, p. 206.

10. Finkelstein, H.: *J. Bone & Joint Surg.* 12:509, 1930.

was, however, finally dismissed, and the patient was operated on under general anesthesia on Nov. 21, 1936, with the provisional diagnosis of tumor of the left wrist.

An incision was made over the volar aspect of the wrist, extending slightly over the thenar eminence, apparently in the region of the flexor carpi radialis tendon. This tendon was cut down on, and a very definite lime salt incrustation



Fig. 5 (case 9).—*A*, anteroposterior view, showing a small, oval, calcific shadow between the greater multangular and the navicular bone. *B*, lateral view, showing the volar position of the radio-opacity, which at operation was found to be a calcification in the sheath of the tendon.

was found within the substance of its sheath. The incrustation was removed in toto and the wound closed in layers. Because of the small size of the incision, there appears to have been some doubts as to the exact tendon about which the calcification was found. This is, of course, immaterial. The important point is, as Dr. Steindler assured us in another letter, under date of March 3, 1937, that

"the calcium deposition was in the sheath of the tendon." He stated: "After removal of the mass the tendon was seen to be smooth and grossly uninvolved in the pathologic process. The site of the involvement was not at the origin or the insertion of the tendon. Preoperatively, there was little or no impairment of the action of the tendon. The calcium deposition was palpable beneath the skin as a small mass and was tender. The patient at this date still experiences complete relief."

Roentgenographically, this case resembles those which we have presented. Yet the duration of the symptoms and the absence of typical limitation of motion raise the question as to whether a fundamental difference may not exist in spite of the superficial resemblance. That calcification does occur in tendons or muscles is sufficient justification for the belief that it may have occurred there in these cases. Obviously, however, final pathologic designation of the clinical condition must be deferred until further microscopic studies have clarified the issue.

No definite etiologic factor can be established. Case 1 certainly seems to suggest an infectious origin. On the other hand, in the case reported by Cohen and in our cases 3 and 5 the symptoms are so definite that the relation of trauma or overuse cannot be denied. In the other cases, such a definite traumatic etiology could not be established, though it seems to be of more than casual significance that the prominence of the pisiform bone, into which the flexor carpi ulnaris tendon is inserted, is the area which is normally brought into contact with the desk or table top. It is comprehensible, therefore, that this region may be subjected to traumas of such a minimal nature as to be unremembered and unrecognized, while still causally related to the onset of symptoms. Because of the abrupt mode of onset of the symptoms and their rapid subsidence under treatment, a traumatic origin seems likely, but an underlying focus of infection, a rheumatic diathesis or a metabolic disturbance cannot be categorically excluded.

Apart from the tenderness, swelling and limitation of motion which have been described in the case histories, the characteristic feature is, of course, the appearance of the radio-opaque substance situated near the pisiform bone. Though we have ventured the diagnosis on a clinical basis, even in the absence of any radiodensity, its presence must be considered as pathognomonic of the condition. The calcific shadow may appear as a delicate lacework or in more solid masses. It may be circular, oval or elongated. In all probability, the size and shape of the shadow depend on the stage of the process and the intensity of the reaction. That the appearance had not been previously noted in thousands of plates examined for other conditions would seem proof of the fact that the calcification was not a casual finding or one which might have antedated or even been the cause of the development of symptoms. This seems to be further substantiated by the fact that the calcification disappeared with the subsidence of the clinical symptoms.

Clinically, the condition must be differentiated from a stenosing tendovaginitis or an acute infectious process, such as cellulitis or osteomyelitis. Roentgenographically, it must be differentiated from osteomyelitis or periostitis of the pisiform bone, an accessory carpal ossicle,

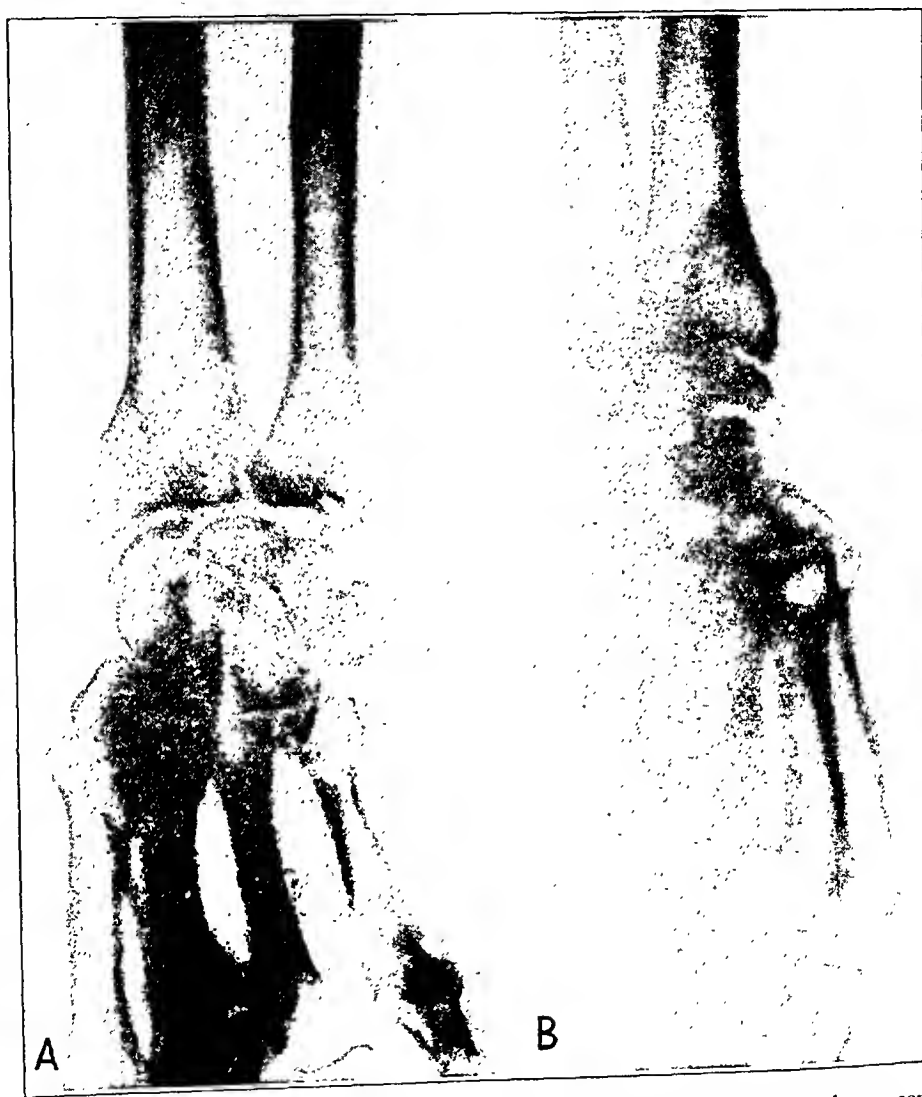


Fig. 6.—*A*, anteroposterior view, showing radio-opacities simulating those seen in the other figures. The patient had a history of a Colles fracture, with fracture of the ulnar styloid process. *B*, on lateral view the radio-opacities were found dorsally and ventrally situated, probably representing fragmentation and healing in a fractured ulnar styloid process.

or an old, comminuted fracture of the ulnar styloid. In the case of one patient whom we recently examined there was a definite history of fracture (fig. 6). Careful lateral and oblique roentgenograms dem-

onstrated conclusively that the ulnar styloid process had been broken at the base and that the calcification was on the dorsal, not the volar, aspect of the wrist. The value of lateral and oblique roentgenograms in all cases cannot be too strongly stressed.

Much as we should welcome the information that would accrue from surgical exploration, we have not found such therapy justifiable. Usually, simple rest on a splint, application of heat and administration of salicylates have resulted in prompt disappearance of the symptoms. It appears that in cases in which the symptoms have been prolonged and in which surgical intervention has finally led to cure the pathologic process has been located in the peritendinous tissue. Though we are not prepared to defend this thesis, the therapeutic response may represent a fundamental pathologic difference and may be a means of clinically differentiating between tendinitis and peritendinitis.

#### CONCLUSION

The number of cases reported is not sufficiently large to permit any elaborate conclusions. Nevertheless, we believe that calcification at the insertion of the flexor carpi ulnaris tendon is a distinct clinical entity and that the outlines of the clinical picture will be found to conform in general with that here delineated. We feel justified in believing that the process which has been described is occasionally due to trauma and is similar to that already well known in the supraspinatus and gluteal muscles. We are of the opinion that the condition is localized not in the bursa but in the tendon. Though the process is not suppurative, in the acute phase it may give rise to lymphangitis and a febrile reaction and may simulate a destructive process of the pisiform bone. The condition is of short duration and apparently always yields readily to treatment with heat, immobilization and salicylates.

NOTE.—Since this paper was submitted for publication five similar cases have been called to our attention. The details are not presented, since they add nothing to what has already been said.

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# CHANGES IN THE MAMMARY GLAND OF THE RAT PRODUCED BY VARIOUS GLANDULAR PREPARATIONS

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During our recent investigation <sup>1</sup> of the influence of endocrine substances on the development of the mammary gland of the rat, a number of mammary abnormalities were experimentally induced. The possibility that some of these observations may have a bearing on diseases of the human breast made it desirable to study the changes further.

It is our purpose in this paper to present the more pertinent results and to suggest their possible relation to mammary disease in human beings.

A number of workers have observed abnormalities in the mammary glands of animals into which various endocrine substances were injected. Evans and Simpson <sup>2</sup> noted extensive mammary development following injection, for long periods, of pituitary extracts into rats; excessive epithelial proliferation and formation of fibro-adenoma occurred in non-castrated females. No effect was obtained in castrates, since the changes are mediated through an effect on the ovaries. Howard <sup>3</sup> recently obtained similar results in noncastrated adult female rats treated for several months with pituitary preparations or with extracts of the blood of pregnant women.

Marked abnormalities of the mammary gland resulting from excessive estrogenic stimulation have been reported. Goormaghtigh and

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This study was aided by a grant from the Anna Fuller Fund.

From the Surgical Pathological Laboratory, Department of Surgery, Johns Hopkins Hospital and Johns Hopkins University School of Medicine.

1. Astwood, E. B.; Geschickter, C. F., and Rausch, E. O.: Development of the Mammary Gland of the Rat: A Study of Normal, Experimental and Pathologic Changes and Their Endocrine Relationships, *Am. J. Anat.* **61**:373, 1937.

2. Evans, H. M., and Simpson, M. E.: Hormones of the Anterior Hypophysis, *Am. J. Physiol.* **98**:511 (Oct.) 1931.

3. Howard, N. J.: Comparative Studies of Gonadotropic Hormones: V. Growth Response of Rat Mammary Glands in Chronic Experiments, *Proc. Soc. Exper. Biol. & Med.* **34**:732 (June) 1936.

Amerlinck<sup>4</sup> produced dilatation of the ducts and adenomatous formations in mice given small doses of estrogen for long periods. Burrows<sup>5</sup> found that continued treatment of mice with estrogen caused the appearance of clusters of acini, dilatation of the ducts, cysts, hyperplasia of the epithelium of the ducts and an increase in stroma. He expressed the opinion that such a series of events is analogous to the chronic cystic mastitis of human beings and stated that mice so treated are more liable to the development of cancer than are nontreated animals. Bonser<sup>6</sup> found that of male mice treated with estrogen, the strains susceptible to cancer showed localized acinar proliferation with subsequent development of cancer while in the strains not susceptible there developed a widespread acinar proliferation without malignant change. Macdonald<sup>7</sup> observed dilatation of the ducts with epithelial proliferation in rabbits treated for three months with estrogen. When such treatment was continued for six months the abnormalities disappeared, and the hypertrophied glands regressed to the resting state, despite continued administration of estrogen. Cystic changes in the mammary glands of rats were obtained by Herold and Effkemann.<sup>8</sup> Gardner, Smith and Strong<sup>9</sup> showed that large doses of estrogen in rats caused a stunted growth of mammary ducts with excessive epithelial proliferation, lobular growth, cystic dilatation of ducts and the appearance of adenomatous areas. Geschickter, Lewis and Hartman<sup>10</sup> induced abnormal mammary growth in the male monkey by the administration of estrogen.

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4. Goormaghtigh, N., and Amerlinck, A.: *Realisation expérimentale de la maladie de Reclus de la mamelle chez la souris*, Bull. Assoc. franç. p. l'étude du cancer **19**:527 (July 15) 1930.

5. Burrows, H.: *Pathological Changes Induced in the Mamma by Estrogenic Compounds* (Hunterian Lecture), Brit. J. Surg. **23**:191 (July) 1935.

6. Bonser, G. M.: *Effect of Estrone Administration on the Mammary Glands of Male Mice of Two Strains Differing Greatly in Their Susceptibility to Spontaneous Mammary Carcinoma*, J. Path. & Bact. **42**:169 (Jan.) 1936.

7. Macdonald, I. G.: *Response of the Mammary Gland to Prolonged Stimulation with Ovarian Hormones*, Surg., Gynec. & Obst. **63**:138 (Aug.) 1936.

8. Herold, L., and Effkemann, G.: *Beziehungen des Follikelhormons zu pathophysiologischen Wachstumsvorgängen der Brustdrüse: I. Brustdrüsenentwicklung unter gesteigerter Zufuhr von Follikelhormon bei der Ratte*, Arch. f. Gynäk. **163**:85, 1936; *II. Tierexperimentelle Untersuchungen über die Bedeutung einer langdauernden und vermehrten Follikelhormonwirkung in der Genese der Fibrosis mammae cystica*, *ibid.* **163**:94, 1936; *III. Unterschiedliche Wirkung einer langdauernden Follikelhormonzufuhr auf die Brustdrüsenstruktur kastrierter und nichtkastrierter Ratten*, *ibid.* **163**:309, 1936.

9. Gardner, W. U.; Smith, G. M., and Strong, L. C.: *Stimulation of Abnormal Mammary Growth by Large Amounts of Estrogenic Hormone*, Proc. Soc. Exper. Biol. & Med. **33**:148 (Oct.) 1935.

10. Geschickter, C. F.; Lewis, D., and Hartman, C. G.: *Tumors of the Breast Related to the Estrin Hormone*, Am. J. Cancer **21**:828 (Aug.) 1934.



The effect of estrogen on the incidence of mammary cancer has been variously reported. Lacassagne<sup>11</sup> in an extensive series of articles described the effect of estrogen on male mice of certain strains, the females of which are highly susceptible to spontaneous cancer of the breast. These males, after extensive development of the mammary gland similar to that of normal females, showed epithelial proliferation, dilatation of the ducts and, after six to eighteen months, malignant change. These experiments seem to show that the feminization of males with mammary development places them in the genetic category of their sisters and that both males and females inherit the predisposition to cancer. Similar results have been obtained by Cramer and Horning<sup>12</sup> and by Gardner, Smith, Allen and Strong.<sup>13</sup> This subject has been thoroughly covered recently by Suntzeff, Burns, Moskop and Loeb,<sup>14</sup> who found that treatment with estrogen modifies the incidence of mammary cancer in susceptible strains. It has not yet been established that estrogenic treatment will initiate the formation of cancer in otherwise nonsusceptible animals.

The relation of mammary diseases in human beings to abnormalities of the female reproductive organs has recently been reviewed by Taylor,<sup>15</sup> who attempted to correlate pain in the breast and formation of tumor with ovarian dysfunction. These studies should lead to further investigation of the mammary changes which so commonly occur in persons who present other evidence of endocrine dysfunction.

#### VARIATIONS IN MAMMARY STRUCTURE

An important consideration in the evaluation of abnormal changes in the breast is variation in the histologic picture and in the physiologic response in different portions of the same breast. In the human breast structural differences in various parts of the gland are difficult to interpret because of the complex distribution of the ducts and the density

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11. Lacassagne, A.: Hormonal Pathogenesis of Adenocarcinoma of the Breast, *Am. J. Cancer* **27**:217 (June) 1936.

12. Cramer, W., and Horning, E. S.: Experimental Production of Estrin of Pituitary Tumors with Hypopituitarism and of Mammary Cancer, *Lancet* **1**:247 (Feb. 1) 1936.

13. Gardner, W. U.; Smith, G. M.; Allen, E., and Strong, L. C.: Cancer of the Mammary Glands Induced in Male Mice Receiving Estrogenic Hormone, *Arch. Path.* **21**:265 (March) 1936.

14. Suntzeff, V.; Burns, E. L.; Moskop, M., and Loeb, L.: Effect of Injections of Estrin on the Incidence of Mammary Cancer in Various Strains of Mice, *Am. J. Cancer* **27**:229 (June) 1936.

15. Taylor, H. C., Jr.: Relation of Chronic Mastitis to Certain Hormones of the Ovary and Pituitary and to Coincident Gynecological Lesions: I. Theoretical Considerations and Histological Studies, *Surg., Gynec. & Obst.* **62**:129 (Feb.) 1936; II. Clinical and Hormone Studies. *ibid.* **62**:562 (March) 1936.

of the enveloping fibrous tissue; but that such local differences exist is shown, for example, by the frequency of certain changes in the outer upper quadrant of the breast and by the fact that markedly different histologic pictures can be seen in a single microscopic preparation from apparently normal breast tissue.

In the normal rat structural differences in various areas of the same mammary gland are very distinct. When the animal is subjected to certain endocrine stimuli, the structure of these areas departs still further from the normal. In the region near the nipple where the single main duct divides into its several larger branches there is a maximum number of small twigs and buds, which respond to estrogenic stimuli



Fig. 1.—Whole mount ( $\times 5\frac{1}{3}$ ) of two mammary glands from a 115 day old female rat treated from birth with 0.25 mg. of testosterone propionate daily. The difference in response in different areas is well shown. The central areas resemble those of the normal male structure, while the periphery is typically female in appearance.

with the formation of small, imperfectly shaped lobules. Throughout the major portion of the gland in the normal female the ducts are regularly distributed and show frequent branching and an even scattering of fine twigs. In the outermost borders of the gland—and this is especially true of the dorsal prolongation of the large abdominal gland—the ducts are irregular, fine and relatively bare; they respond in a limited manner to estrogenic stimuli and, as noted by Maeder,<sup>16</sup> even to the

16. Maeder, L. M. A.: Changes in the Mammary Gland of the Albino Rat (*Mus Norvegicus Albinus*) During Lactation and Involution, *Am. J. Anat.* **31**:1 (Sept.) 1922.

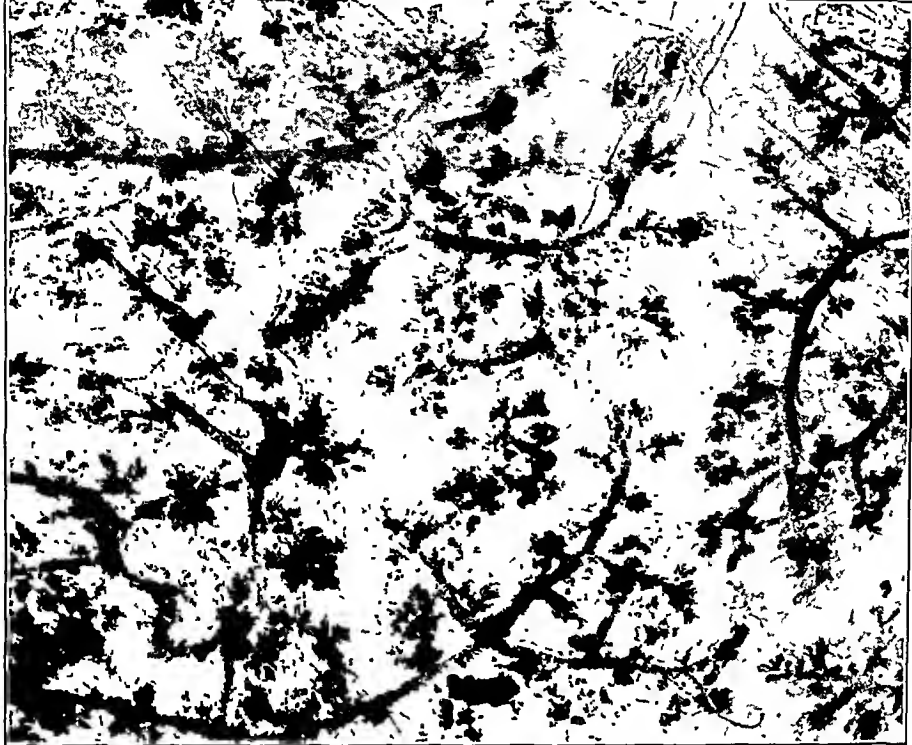


Fig. 2.—Whole mount ( $\times 18$ ) of a mammary gland of a normal 75 day old female rat, showing the normal postpuberal architecture characteristic of the non-pregnant adult female.

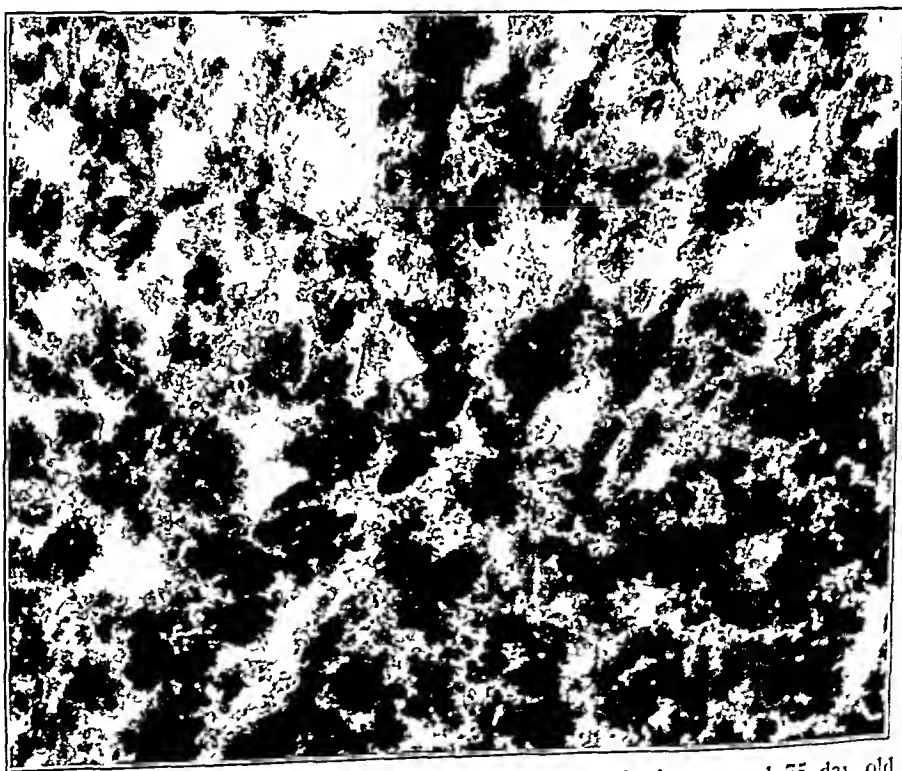


Fig. 3.—Whole mount ( $\times 18$ ) of a mammary gland of a normal 75 day old male rat, showing the characteristic dense structure made up of lobule-like acinar clumps.

stimulus of pregnancy. When normal this region is easily mistaken for a region of regression. Figure 1 shows a mammary gland of a female rat treated from birth with 250 micrograms of testosterone propionate for one hundred and fifteen days. The central area near the nipple, consisting largely of the main ducts, has responded well to the androgenic stimulus, while the peripheral regions show little effect of the preparation.

#### SEXUAL DIFFERENCES

Differences between the early development of the male and that of the female breast, as noted by Myers,<sup>17</sup> consist chiefly in the distribution of the main ducts. In most respects development during early life is identical in the two sexes; marked sexual differences in the rat appear after six weeks under the influence of the developing gonad, as described by Turner and Schultze.<sup>18</sup> In the female the influence of the developing ovary results in a rapid extension of the duct tree and a multiplication of fine twigs (estrogenic stimulation), as seen in figure 2, while in the mature male the finer mammary ducts terminate in a proliferation of acinar elements, which results in the small dense gland characteristic of the adult male rat (influence of androgen), as seen in figure 3. In animals which are castrated at the age of 21 days, increase in size is not interfered with during the next three weeks; but after the sixth week of life the glands begin to grow more slowly, and after the eighth week they show signs of regression. At this stage differences between the male and female glands are most marked. The female gland shows a profusion of extremely fine branched ducts, which cover an extensive area, while the male gland, smaller in extent, is composed of thicker, more irregular and less numerous branched ducts (figures 4 and 5). These differences are entirely independent of the gonad and must be classed as genetic sexual differences. Such sexual differences undoubtedly are present also in the human being, and one might expect unsimilar responses in the two sexes to administration of glandular preparations. This has already been indicated by the unusual type of mammary growth occasionally induced in the human male by large doses of estrogen.<sup>19</sup>

The changes effected in the breast by an endocrine stimulus are dependent as much on the inherent behavior of the breast as on the nature of the stimulus. In general, the male breast responds to estrogenic stimuli in a manner comparable to that of the female, that is,

17. Myers, J. A.: Studies on the Mammary Gland: III. A Comparison of the Developing Mammary Glands in Male and Female Albino Rats from the Late Fetal Stages to Ten Weeks of Age, *Anat. Rec.* **13**:205 (Sept.) 1917.

18. Turner, C. W., and Schultze, A. B.: A Study of the Causes of the Normal Development of the Mammary Glands of the Albino Rat, Research Bulletin 157, University of Missouri, College of Agriculture, Agricultural Experiment Station, 1931.



Fig. 4.—Whole mount ( $\times 18$ ) of a mammary gland of a 75 day old female rat whose ovaries were removed at the age of 21 days. The ducts are fine and bare and do not show the profusion of fine twigs and buds which result from ovarian maturation, as seen in figure 1.

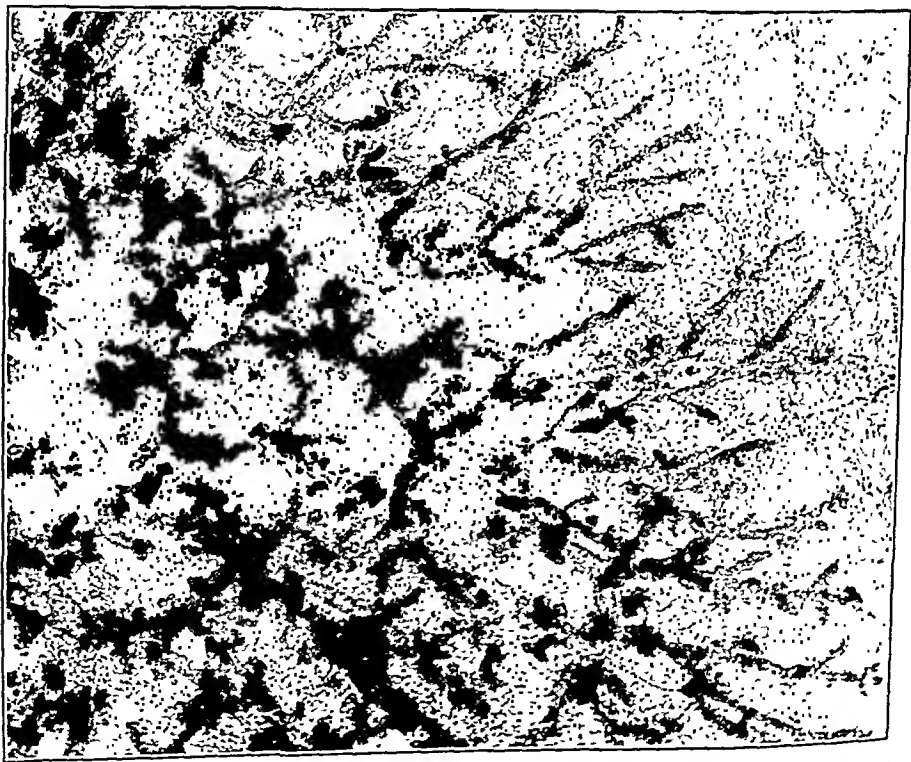


Fig. 5.—Whole mount ( $\times 18$ ) of a mammary gland of a 75 day old male rat castrated at the age of 21 days. The ducts are wider and possess more clublike branches and buds than those of the castrated female shown in figure 2. The dense growth of lobule-like structures due to testicular influence is not present. Compare with figure 3.

through extension and increased branching of the duct tree. In a series of experiments with the undeveloped glands of immature animals, little difference can be seen in the effect of estrogen on the male and on the female. When estrogen is administered for longer periods, some differences become apparent. The male glands show a greater tendency to form clumps of alveolar structures, while the female glands respond by more marked extension of the duct tree.

Thus the difference in structure and in manner of response in various portions of the same gland and the difference between the behavior of the glands in male and female castrates show that a large part of the response mechanism rests in the gland itself and is entirely independent of the stimulus to growth. This local variation in response must be constantly borne in mind when one is interpreting the abnormalities experimentally induced, particularly in the evaluation of the results of studies of the human mammary gland.

#### EXCESSIVE ESTROGENIC STIMULATION

The typical effect of estrogen on the mammary gland is well shown in the immature rat; there is an easily recognizable extension of the duct tree, with increased branching. This response is characteristic of estrogenic stimulation, is distinct from other hormonal effects and is a sensitive index of estrogenic activity, 1 international unit of estrogen given daily producing a notable effect. This physiologic effect of estrogen on the breast in causing extension of the duct tree appears to be common to all species studied. In the human being a similar response is seen in the rapid growth of ducts early in puberty in the female. The human breast, however, possesses a large amount of fibrous stroma and in this respect is peculiar among mammals. Therefore, the mechanism of this growth of fibrous tissue cannot be adequately studied in any mammal except the human being.

The lobular formation of pregnancy cannot be produced in the castrated rat by estrogen alone, this substance merely producing an extension of the system of ducts, with a profusion of fine twigs and buds. That is to say, estrogen produces a mammary gland typical of the adult female virgin state, while the changes of pregnancy are due to mechanisms which are as yet poorly understood. In certain species, for example, the guinea pig,<sup>19</sup> estrogen alone is capable of stimulating formation of lobules. We have found this to be the case in monkeys at puberty, and it seems probable that it is also true of the human being.

19. Nelson, W. O.: Studies on the Physiology of Lactation: VI. The Endocrine Influences Concerned in the Development and Function of the Mammary Gland in the Guinea Pig, *Am. J. Anat.* **60**:341 (March) 1937.

Giving more than the physiologic dose of estrogen or prolonging administration results in certain constant and definite abnormalities. These are probably due not to a direct action of estrogen but rather to a profound upset in the endocrine mechanism which controls mammary growth. Large doses of estrogen show their earliest effects in causing a stunted type of growth. The duct tree is less extended than with small doses and becomes more irregular; the ducts are distorted and widened, with irregular club-shaped twigs along their length. From the first there is evidence of excessive epithelial growth, especially in the

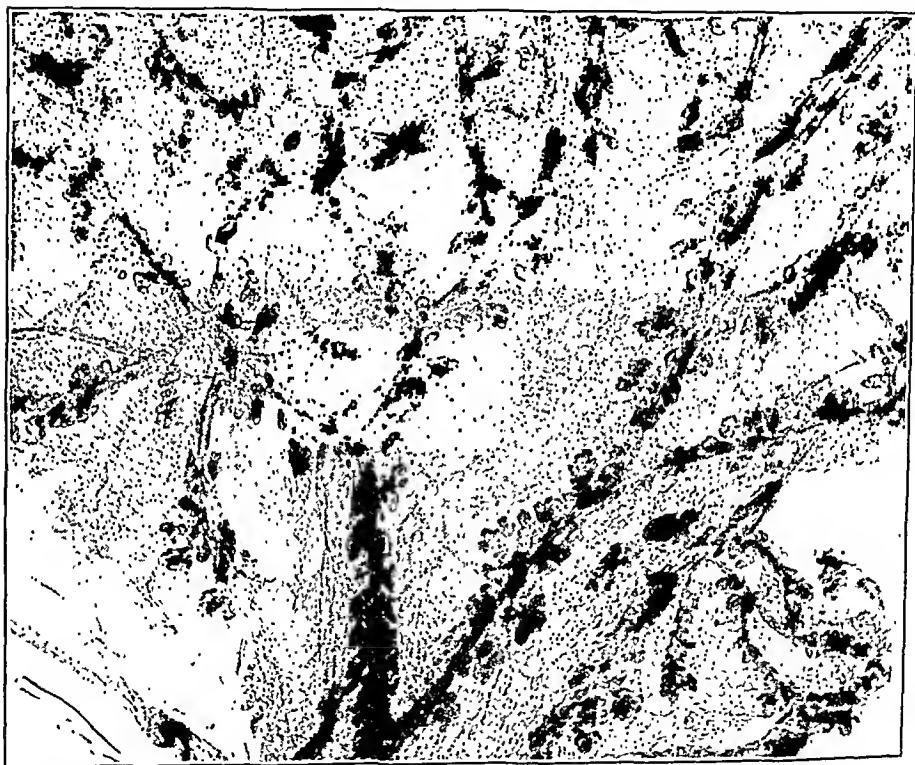


Fig. 6.—Whole mount ( $\times 18$ ) of a mammary gland of a female rat castrated at the age of 21 days and treated for nine days with 100 micrograms of estrone daily, showing the earliest effect of high doses of estrogen. The ducts are widened, and there is excessive proliferation of buds and short branches. The gland was restricted in area.

terminal buds and smaller twigs, and accompanying this growth there appears evidence of secretory activity. Figure 6 shows the breast of a rat castrated at the age of 21 days and treated for nine days with 100 micrograms of estrone daily; the widening of the short, irregular ducts and the accumulation of budlike projections can be seen. This early dwarfing can be readily accentuated by more vigorous treatment; it is distinctly pathologic.



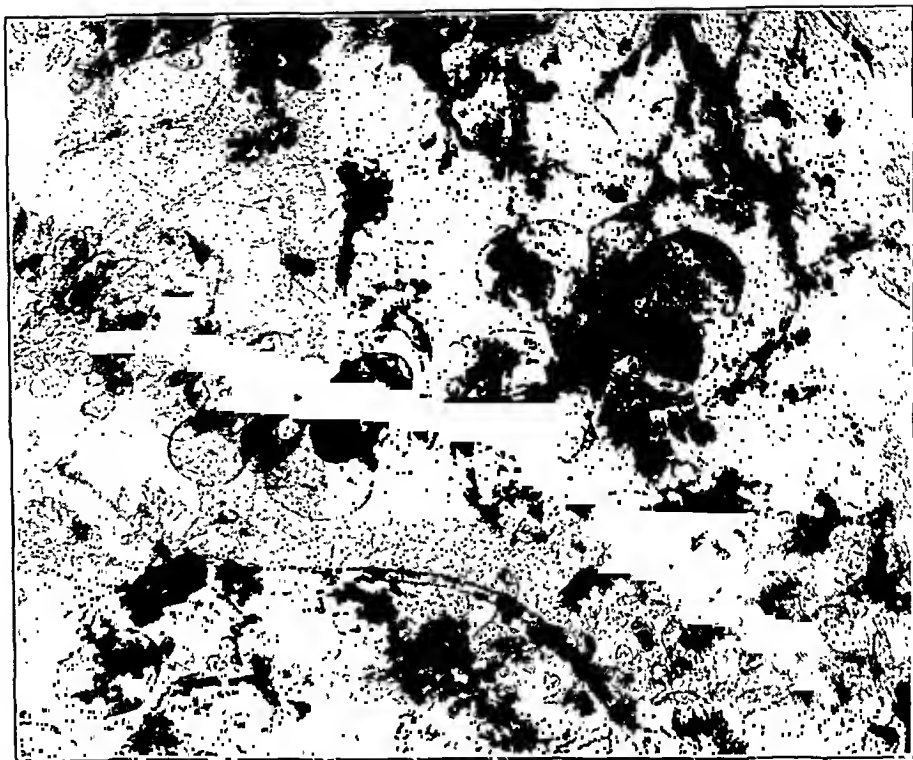


Fig. 7.—Whole mount ( $\times 18$ ) of a mammary gland of a female rat castrated at the age of 21 days and given 200 micrograms of estrone daily for fifty-six days, showing the formation of cysts in the terminal buds and side branches of the moderately dilated ducts.



Fig. 8.—Whole mount ( $\times 5\frac{1}{3}$ ) of a mammary gland of a female rat castrated at the age of 21 days and given 200 micrograms of estrone daily for one hundred and fifty days, showing an advanced stage of cyst formation. The larger cysts appear as dark areas and the smaller ones as small grapelike clusters. The cysts (fig. 10) contain coagulated secretion and are lined by proliferating epithelium. An unaffected area is seen in the usual refractory zone on the left.



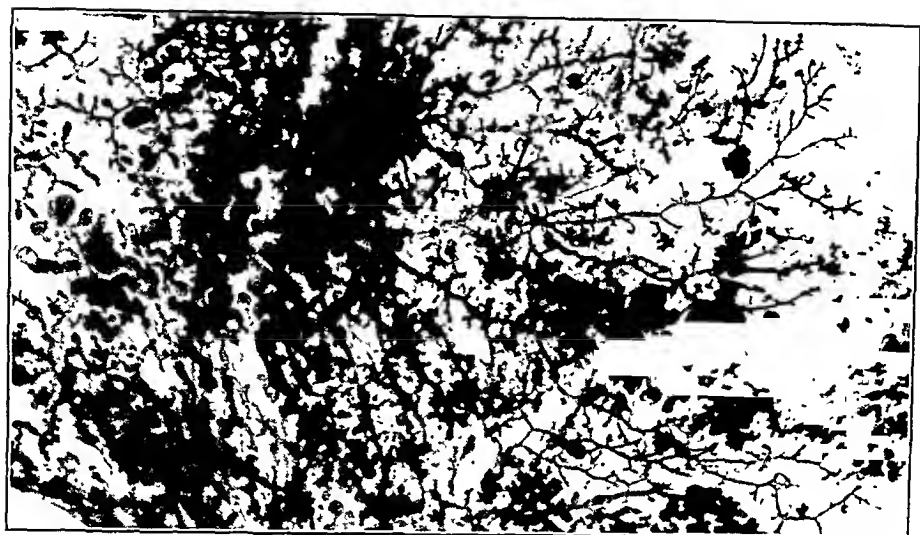


Fig. 9.—Whole mount ( $\times 3$ ) of a mammary gland of a rat castrated at the age of 21 days and given 50 micrograms of estrone daily for one hundred and ninety-three days, showing the formation of small cystic dilatations and irregular epithelial buds resulting from prolonged dosage with moderate amounts of estrogen.



Fig. 10.—Paraffin section ( $\times 27$ ) of a portion of the mammary gland shown in figure 8. In this area the small cysts are nearly filled with epithelial growth and small papillomas. The picture is not unlike that of Schimmelbusch's disease in human beings.

When such excessive doses of estrogen are continued, marked evidence of secretion becomes manifest. The ducts become widened; the budlike projections are distended, and cysts of all sizes appear. These



Fig. 11.—Paraffin section ( $\times 27$ ) of a mammary gland from the animal shown in figures 8 and 10. The largest cyst possesses a thick fibrous wall without an epithelial lining, while the smaller shows a proliferation of fibroblasts invading the contained secretion. The smallest cysts still possess a single orderly layer of epithelium.

cysts are formed in the termini of the ducts, in those structures destined normally to form acini. Figures 7 to 11 inclusive show the appearance

of this cystic change. It can be seen that the smaller cysts are lined by a single layer of epithelium and that their lumens, filled with dense secretion, are in direct communication with the ducts, which are distended with a like secretion. In some areas, after prolonged overstimulation with estrogen, there is excessive epithelial growth in the ducts and in the cyst walls, resulting in a heaping up of cells and papillomatous growths (fig. 10). As the cysts become larger and older they lose their epithelial lining, and the enveloping fibrous tissue becomes more dense, surrounding the cavity as a thick wall. At this stage the original communication of the cyst cavity with the lumen of the duct is lost, and the contents can no longer be expressed without rupture of the cyst wall. Some of the cysts show excessive proliferation of fibrous tissue in their walls, while invasion of the lumen by fibroblasts gives the appearance of organization of the contained secretion (fig. 11). These cystic changes have been constantly observed in all animals receiving 100 or more micrograms of estrone daily for periods of three weeks or more, and in those animals given 50 micrograms daily for longer periods, in which they occur less often or are smaller. It has been found that the higher the dose, the more quickly the cysts develop, and the more marked is the degree of abnormal change. In animals receiving these large doses of estrogen the cystic changes can be prevented, as will be seen later, by administering other hormones.

Smaller doses of estrone given over long periods result in a different type of mammary change. Doses such as 25 micrograms daily or 100 to 200 micrograms *weekly* produce a primary stimulation of development of duct and terminal tubules marked by evidence of excessive epithelial growth. Secretory phenomena are minimal; only after long periods of treatment are cystic dilatations noted, and even then they are not marked. Instead, the primary picture of estrogenic stimulation gradually gives way to the appearance of regressive changes. The mammary gland becomes more and more varied in its architecture, and the differences noted in different regions of the normal gland are greatly accentuated. Certain regions show marked involution, with narrow, crooked bare ducts; in other regions the ducts are distended with clear secretion, and their budlike projections are dilated into microscopic cysts. Scattered throughout most of the gland are isolated areas of terminal tubular proliferation resulting in clumps of imperfectly formed lobules; occasionally one or two normal-appearing lobules made up of discrete alveoli are seen. Figure 12 shows an area of excessive epithelial proliferation in a castrated female rat treated from the twenty-

first day of life with 25 micrograms of estrone daily for fifty-six days. The growth of terminal tubules is extremely irregular; in some places clumps of tubules form dense epithelial masses, while in others, discrete lobules result; some of the ducts are devoid of tubular growth for a part of their length. Other areas of this same mammary gland showed marked regression similar to that of the castrated female rat pictured in figure 4. Treatment with estrogen for long periods produces an increase in the amount and density of the periductal connective tissue. Normally very

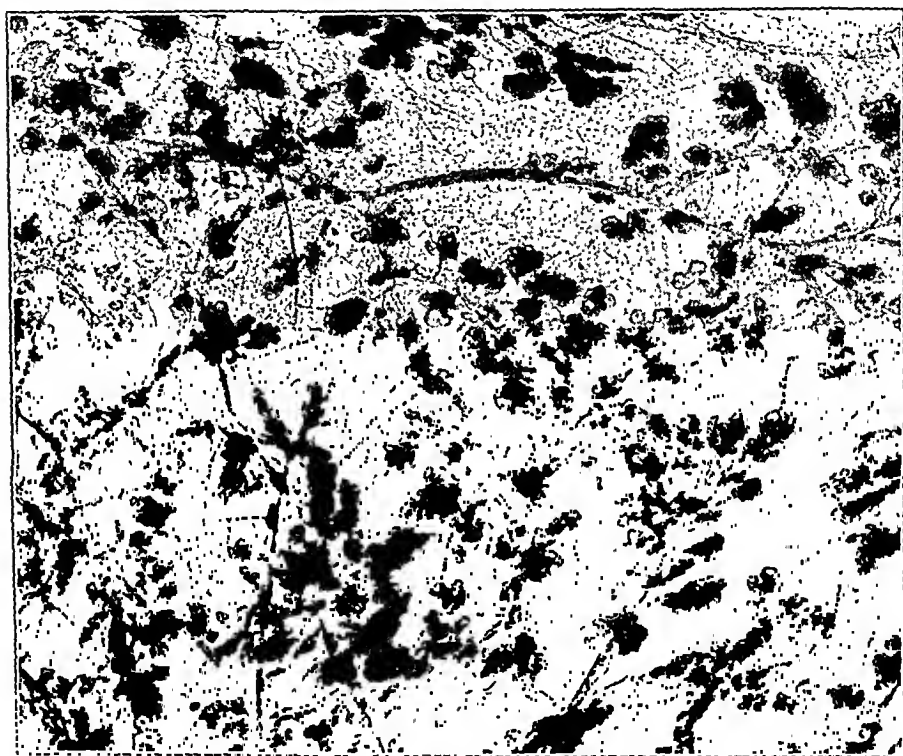


Fig. 12.—Whole mount ( $\times 18$ ) of a mammary gland of a female rat castrated at the age of 21 days and given 25 micrograms of estrogen daily for fifty-eight days, showing an area of extensive epithelial proliferation. The lobule-like structures are irregular and isolated, leaving many parts of the ducts bare. Other regions in this gland resembled regions seen in figure 4.

fine and areolar, scarcely demarcating the duct from the surrounding fatty stroma of the breast, the periductal connective tissue becomes thickened and opaque, encasing the ducts in a dense tube of fibrous tissue. This change is most marked near the nipple, around the larger ducts, becoming less perceptible toward the periphery of the gland. Figures 13 and 14 show increased connective tissue, around the main ducts, small

cysts, areas of epithelial proliferation and adenoma-like formation in a rat treated for six months with 50 micrograms of estrogen daily.

The changes which follow the administration of various amounts of estrogen are similar to that group of conditions in the human breast included in the term chronic mastitis. The pathologic changes of these diseases of the breast are extremely varied, but there is reason to believe that they are all attributable to a single mechanism, and for the most part the individual changes are but different degrees and different stages of the same abnormal process. Although proof is lacking, it would



Fig. 13.—Paraffin section ( $\times 27$ ) of a mammary gland of a female rat castrated at the age of 21 days and given 50 micrograms of estrogen daily for one hundred and eighty-five days. In this area can be seen dilatation of the ducts, with increased periductal connective tissue, cystic formation, excessive intracystic epithelial proliferation and an area of adenomatous growth.

appear that the formation of large cysts in the breasts of rats given more than 100 micrograms of estrone daily for several months is analogous to that form of cystic disease characterized by the presence of a limited number of large cysts (the blue-domed cyst of Bloodgood). In this condition there is little formation of lobules, and a minimum of epithelial proliferation occurs.

Those histologic changes in the breast of the rat which result from the administration of estrogen for longer periods, i. e., for six months or more, in smaller doses closely resemble the more diffuse mammary

changes common to the earlier phases of all forms of chronic cystic mastitis. In these cases there is great variation in the histologic picture, which in different regions shows dilatation of ducts, cyst formation, epithelial proliferation with intracystic papillomas, areas of

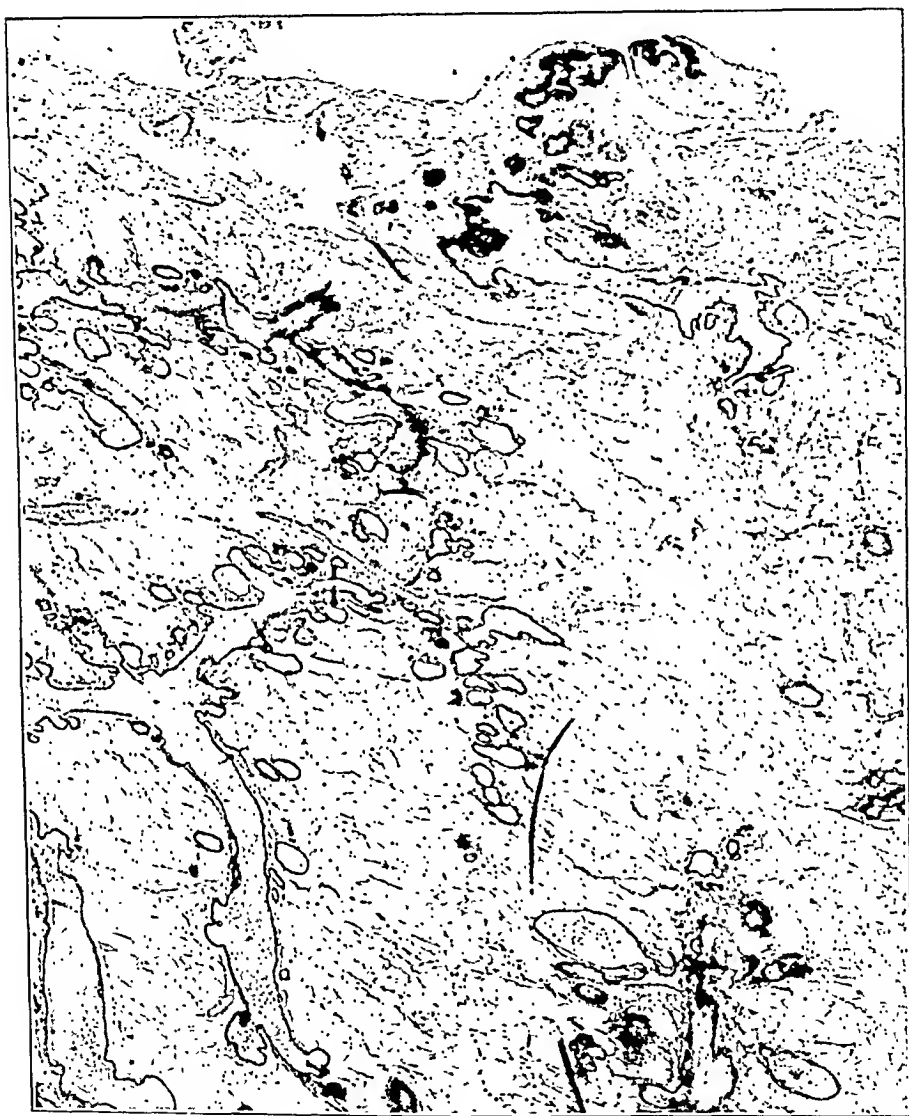


Fig. 14.—Paraffin section ( $\times 27$ ) of a mammary gland of the rat from which was taken the section presented in figure 13, showing an area around the larger ducts near the nipple, where there is a considerable increase in periductal connective tissue.

lobule formation resembling localized adenomas and a generalized increase in fibrous stroma. The marked epithelial proliferation in the animals which receive estrogen for long periods resembles that seen in

the form of chronic cystic mastitis first described by Schimmelbusch, in which the small mammary gland with its short ducts shows extensive epithelial overgrowth, formation of adenomas and papillomas being concurrent with the cystic change. It must be remembered, however, that in the human being there is a difference in response to estrogen on the part of the fibrous stroma and of the lobular epithelium. The lobular growth, as demonstrated in the monkey, may respond more readily to stimulation by the corpus luteum hormone. Therefore, too close a parallel cannot be drawn between the mammary changes in the human being and those experimentally induced in rats.

#### EFFECTS OF STIMULATING THE GONADS

In contrast to the extension of the duct tree produced by the action of estrogen on the breast, the effect of gonadotropic substances on the intact female is the occurrence of the true changes of pregnancy, with formation of lobules. When the gonadotropic substance from the urine of pregnant women or the gonad-stimulating substance of urine taken from women after the menopause is administered to the rat, marked ovarian enlargement resulting from the formation of numerous large corpora lutea occurs. The mammary glands of animals whose ovaries are thus stimulated are indistinguishable from those of a pregnant animal at full term. Continuation of such treatment will not maintain the mammary gland in such a condition for long periods, for after a month or two the animal becomes refractory to the injected substance, the ovaries decrease in size and the mammary glands regress. The degree to which regression occurs varies greatly in different animals and with different gonadotropic preparations. In most cases involution begins between the first and the second month of injection and slowly continues for a month or more. In some cases the involuted gland is scarcely distinguishable from that of the normal, nontreated animal, but usually there is notable increase in the periductal connective tissue, and frequently there are residual areas of incomplete regression. Figure 15 shows the residual increase in connective tissue after prolonged administration of gonadotropic substance. Sometimes incompletely involuted areas stand out in contrast to the surrounding structures and may be confused with true adenoma or fibro-adenoma.

It is interesting that in animals whose mammary glands are maintained in a state similar to that of pregnancy high doses of estrogen do not produce cystic changes. As has been shown, a daily dose of 100 micrograms or more of estrone resulted in formation of cysts within three weeks in every case. When noncastrated animals are given gonadotropic substances during the period of administration of estrogen, the mammary glands show lobular development and the full changes of preg-

# ARCHIVES OF SURGERY

VOLUME 36

MAY 1938

NUMBER 5

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## INTRA-ABDOMINAL APOPLEXY

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This report will describe in detail only 1 case. However, since the pathologic process involved has been recorded in the literature only rarely, 12 previously reported cases will be tabulated and brief allusion made to them. In referring to intra-abdominal apoplexy, the subject of this report, Graham commented:

This is probably a much more important matter than would seem to be the case from the small amount of discussion which it has received in the literature. Of interest also in this connection is the similarity of the symptoms produced by retroperitoneal hemorrhage to those of an acute surgical intra-abdominal lesion, a point which has been emphasized by Warren H. Cole.

Thompson and Dunphy stated:

Intra-abdominal apoplexy is the spontaneous rupture of an arterio-sclerotic artery of one of the abdominal viscera. In this region it is the counterpart of cerebral hemorrhage, but, whereas the latter condition is common, intra-abdominal apoplexy is either extremely rare or seldom recognized.

As far as I have been able to determine, only 12 instances of this accident have been recorded in the literature. In 9 the condition was discovered at operation and in 3 at necropsy. In the thirteenth case, recorded here, it was discovered at operation.

### REPORT OF A CASE

C. E. B., a white man aged 72, was admitted to the University of Virginia Hospital on March 24, 1936. He complained of severe, generalized cramplike pain in the abdomen, of approximately twelve hours' duration. The abdominal discomfort was so persistent and severe that the patient was referred for surgical consultation. The symptoms first appeared when he awakened in the morning; because he had not had a stool in two days, he attributed the pain to constipation and took a saline laxative. The constipation was not relieved until he received an enema, but even this did not alleviate the pain. He did not have nausea but induced vomiting, which did not relieve him.

Nearly two weeks previously, on March 13, herpes had appeared on his forehead. He had been treated by his physician on three successive days, March 18, 19 and 20, with 1 cc. of solution of posterior pituitary administered subcutaneously.



The herpes had improved promptly, and he had not had any untoward effects or symptoms in connection with the treatment. His history was otherwise unimportant.

The data obtained from examination did not suggest that the patient was very ill. He complained of pain in his abdomen, but it did not seem to be severe. Except in the abdomen, little of an abnormal nature was observed. The rectal temperature was 99.8 F.; the pulse and respiratory rates, normal. The blood pressure was not recorded. The abdomen was slightly distended and a little tender throughout, though there was no spasm of the muscles. No masses were palpable, and no signs of fluid were present. Examinations in the laboratory did not reveal any abnormalities. The hemoglobin content was 80 per cent (Dare), the erythrocyte count 4,020,000, the leukocyte count 8,200 and the differential count normal. The urine contained no abnormal constituents, and the Wassermann and Kahn reactions of the blood were negative.

*Instances of Intra-Abdominal Apoplexy Recorded in the Literature*

No.	Year	Author	Sex	Age	Data			
					Anatomic Location	Operation	Result	Autopsy
1	1913	Florence and Ducuing..	F	..	Sup. mesent. art.	No	Died	Yes
2	1918	Hilliard.....	M	48	Transy. mesocolon	Yes	Died	No
3	1923	Starecke.....	M	60	Gast.-duod. art.	Yes	Recovered	No
4	1925	Budde.....	M	27	L. gast.-epip. art.	Yes	Recovered	No
5	1931	Green and Powers.....	F	54	L. gast. art.	Yes	Recovered	No
6	1933	Mourgue - Molines and Cabanac	M	56	L. gast. art.	Yes	Recovered	No
7	1933	Mourgue - Molines and Cabanac	..	..	L. gast. art.	Yes	Recovered	No
8	1933	Mourgue - Molines and Cabanac (Rud)	F	73	L. gast.-epip. art.	Yes	Died	Yes
9	1935	Thompson and Dunphy	F	62	L. gast. art.	Yes	Recovered	No
10	1935	Buchblinder and Greene	M	57	R. gast. art.	Yes	Recovered	No
11	1936	Moorehead and McLester	M	44	R. and l. gast. art.	No	Died	Yes
12	1936	Moorehead and McLester	M	50	Sup. mesent. art.	No	Died	Yes
13	1938	Morton	M	72	Sup. mesent. art.	Yes	Recovered	No

During two days in the hospital, the patient's symptoms gradually subsided, and the distention and tenderness in the abdomen disappeared almost entirely. The tenderness, however, persisted to a slight degree, in the lower part of the abdomen on the right side more than elsewhere. It was therefore thought that the patient might have had a mild attack of appendicitis, although a positive diagnosis was not made at that time. Accordingly, when he was discharged, he was advised to restrict his diet somewhat, to avoid the use of laxatives and to report immediately if the symptoms reappeared.

Nothing further was heard from him until five days later, March 30. His wife telephoned early in the morning to relate that he had been awakened by severe cramps in the abdomen. He was at once readmitted to the hospital. Before coming to the hospital, however, he had taken an enema that had not been effectual or relieved the pain. He had been nauseated and had vomited. The results of examination at the time of readmission were essentially the same as those at the time of the former admission. There was, however, a little more tenderness throughout the abdomen, and in addition there was an indefinite mass to the left of the umbilicus. The patient's temperature was 100 F., and his pulse and respiratory rates were only slightly elevated. It was thought that he probably had an abscess in the left side of the abdomen, possibly the result of diverticulitis.

of the colon. Further observation seemed more desirable than immediate operation. During the day the patient gradually became more comfortable, and the tenderness in the abdomen decreased perceptibly. He spent a reasonably comfortable night, but at 6 a. m. he was seized again with severe cramping pain in the abdomen. About three hours later, rather suddenly, he went into a state of shock. After appropriate measures to combat shock had been employed successfully, plans were made for an immediate exploratory laparotomy.

Operation was performed on March 31. With the patient under anesthesia induced by inhalation of ether, the abdomen was explored through an incision in the middle portion of the rectus muscle on the left side. The incision overlay the mass which had been palpated just to the left of the umbilicus. Immediately on incision of the peritoneum, a large amount of blood escaped. Investigation revealed the presence of much liquid blood as well as a quantity of blood clot throughout the abdominal cavity. It was estimated that there must have been at least as much as 500 cc. of each. There was a hematoma in the root of the mesentery of the small intestine, which was approximately 10 cm. in diameter. The inferior aspect of the hematoma had ruptured and permitted the extravasation of the blood observed in the free peritoneal cavity. The source of the hematoma was obviously a rupture of one of the branches of the superior mesenteric artery, in or near the root of the mesentery. A more exact identification of the vessel was precluded by the nature and location of the lesion. It seemed unwise to tamper with the hematoma and take the chance of starting a fresh hemorrhage or endangering the blood supply to the intestine. Because there was no evidence of active bleeding after the blood and clots had been removed from the abdomen, the incision was closed without any further attempt at operative procedure. The usual suture of the abdominal wall in layers was carried out in the routine manner, and the patient was returned to his room in excellent condition, apparently none the worse for the operation.

Postoperative convalescence was somewhat prolonged by slow healing of the incision, but uneventful. Several transfusions of blood were given at intervals in order to restore the blood lost by hemorrhage. Repeated determinations of blood pressure did not reveal any arterial hypertension. The patient was discharged from the hospital on May 11, forty-one days after the operation. At the time of discharge, he was able to walk about and his general condition seemed to be good. Follow-up reports have been interesting in that the patient apparently has been in as good health since the operative demonstration of intra-abdominal apoplexy as before. He was a patient in the hospital in the medical service for acute infection of the respiratory tract from Dec. 14, 1936, to Jan. 5, 1937. At the time of that admission his blood pressure was 155 systolic and 96 diastolic. At the time of discharge the blood pressure was 100 systolic and 70 diastolic. At the time of writing, more than one year after the occurrence of the hemorrhage, the patient is in good health. He has no complaints referable to the original disease except a slight weakness of the abdominal wall at the site of the operative incision.

#### COMMENT

Reference to the accompanying table and comparison of this case with those previously reported by others do not reveal any striking differences except in the location of the lesion. This is only the third instance in which the hemorrhage has occurred in a branch of the superior mesenteric artery. The age of this man was above the average

in the cases previously reported but not the highest on record, for the patient in 1 case was a year older. As for incidence in the sexes, occurrence in men seems to predominate over that in women by a ratio of 2 to 1. As in all except 3 of the other cases, the diagnosis was made in the course of operation. It is interesting that the correct diagnosis has not been made before operation in a single instance. In the 3 cases in which an operation was not performed, the diagnosis was not made prior to necropsy. In each case in which an operation was performed, the preoperative diagnosis was that of some acute abdominal emergency, such as perforated viscus, acute inflammatory process or acute intestinal obstruction. Of the conditions mentioned as tentative preoperative diagnoses, that most nearly related to the true condition was mesenteric thrombosis. Probably the most interesting fact about abdominal apoplexy is that, in spite of its similarity to cerebral apoplexy, a condition frequently encountered, it has rarely been observed. Of course, it may occur much more frequently than published reports would indicate; nevertheless, even though allowance is made for this discrepancy, the condition must still be rare in comparison with the incidence which might be expected.

The reported cases were almost all those of persons in the period of life in which arteriosclerosis is always present to some degree. In cases in which tissue was examined there was both gross and microscopic evidence of arteriosclerosis. There would seem to be no doubt, therefore, that arteriosclerosis is the underlying pathologic process usually responsible for the rupture of the vessel and the consequent hemorrhage. The precipitating cause of the rupture may be, as in the case of cerebral hemorrhage, unexplainable. Anything that raises blood pressure might well predispose to a blowing out at any previously weakened spot. In the case here reported a pressor drug had been administered hypodermically a few days before the first abdominal symptoms appeared. It seems fair to assume that this drug may have played a part in the rupture of the vessel. On the other hand, it is not uncommon for cerebral hemorrhage to occur while one is asleep, although blood pressure is then presumably at its lowest and most stable level. If one may reason by analogy, one may conclude that there need not be any precipitating cause for the hemorrhage. The vessel wall in a diseased area merely becomes gradually too weak to withstand even normal systolic pressure and finally ruptures. All these considerations still leave unexplained the rarity of intra-abdominal apoplexy.

Spontaneous rupture of an aneurysm within the abdominal cavity is an accident that is pathologically and clinically related to intra-abdominal apoplexy. It occurs much more frequently, however, perhaps because of the difference in effective pressures in the larger and the smaller vessel, and is usually immediately fatal. Instances of rupture of aneurysm of the aorta are not uncommon, and the same is true to a

lesser degree in the splenic and other large arteries within the abdominal cavity. It is possible, of course, that in some of those cases recorded as instances of true intra-abdominal apoplexy the rupture of the vessel may have occurred in a small preexisting aneurysm. If this was the case, however, the pathologic proof of it was overlooked.

The diagnostic problem presented by cases of intra-abdominal apoplexy seems to be almost insurmountable. A correct clinical diagnosis was not made in a single case of all those so far reported in the literature, and that reported here is no exception. An examination of the pathologic process involved and the clinical symptoms does not disclose any characteristic that is sufficiently distinctive to offer much hope for the recognition of cases that may be encountered in the future. It would seem that the condition must be included in the group of acute diseases that warrant surgical exploration of the abdomen because of signs of severe irritation of the peritoneum. If the condition is borne in mind as a possibility when one is dealing with diseases, it is quite possible that it may be occasionally diagnosed, at least presumptively.

Treatment, if one may judge by the reported cases, must usually be surgical. All except 3 of the patients were subjected to operation, and those 3 died rather suddenly of massive hemorrhage. Of those operated on, only 2 of 10 died, 1 at the end of six hours and the other after six days. The operative procedure employed was ligation of the bleeding vessel in 4 instances, while in the other 6 apparently nothing was done. In the case here reported nothing was done because there was no evidence of active bleeding. Moreover, it was feared that to disturb the hematoma at the root of the mesentery of the small intestine would endanger the circulation in the intestine. It seems reasonable to suppose, however, that ligation of the bleeding vessel may in some instances be the means of preventing continued loss of blood and consequent death. Immediate postoperative treatment and later after-care of the patient would not seem to offer any particular problems. General measures to promote a serene life should be advised, just as in the case of cerebral hemorrhage. Pressor drugs should no doubt be avoided. In this connection it is interesting to note that no case of a second attack of intra-abdominal apoplexy has ever been reported, although instances of repeated cerebral apoplexy are common.

#### SUMMARY

Twelve cases of intra-abdominal apoplexy, the spontaneous rupture of an arteriosclerotic artery of one of the abdominal viscera, were found in the literature and are briefly discussed. In connection with them, an additional case, which I encountered, is reported in greater detail. The etiology of the disease, as far as the pathologic process is concerned, seems plain, though its rarity and the factors that may precipitate it

are unexplained. The condition does not seem to have any distinctive characteristics that may lead to a positive diagnosis. It should, however, be thought of as a possibility in any case in which there are signs of peritoneal irritation. Treatment is surgical and should be by ligation of the bleeding vessel whenever practicable.

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# ACUTE RETROCECAL APPENDICITIS

BASED ON SEVEN HUNDRED AND FIFTY-ONE INSTANCES

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In view of the fact that during the past 10 years nearly four thousand articles have crowded the medical literature on the general subject of appendicitis, it is indeed strange that its most dangerous form, namely, acute retrocecal appendicitis, has been so largely neglected. The classic article by Brunn on acute pelvic appendicitis has done much to direct attention to the relation existing between the position of the

TABLE 1.—*Average Distribution in Percentage of Diseased Appendixes According to the Pathologic Condition Encountered*

Author and Year	Number of Cases Reported	Acute Appendicitis with Unruptured Appendix	Acute Appendicitis with Perforated Appendix and Abscess or Localized Peritonitis	Acute Appendicitis with Spreading or Generalized Peritonitis
Various authors,* 1931 to 1937.....	30,593	53.8	30.8	19.4
Collins, 1938.....	751	47.35	31.12	21.42

\* Bower; Finney; Keyes; Weyll and Wallace; Harris; Cayford; Lled; Merrell; Reid, Poer and Merrell; Lamon; Hobler; Pattison; Cook and Beardsley; Rhodes, Birnbaum and Brown, and Sperling and Myrick.

appendix and acute inflammation. Acute retrocecal appendicitis is largely responsible for the atypical signs and symptoms in cases of acute appendicitis that deceive the incautious diagnostician and cause many deaths. In my previous studies it has been proved that most adherent retrocecal appendixes derive their abnormal position from previous attacks of acute appendicitis. Wakeley studied the position of the human vermiform appendix in 10,000 cases. He reported that in 65.28 per cent of his series the appendix was either free or adherent in a postcecal or retrocecal position. In a study published in 1932, on postmortem examinations of 4,680 appendixes, I noted that only 20.21 per cent were fixed in a retrocecal situation. Meyer and Spivack studied 370 cadavers and observed that 9.5 per cent of the appendixes were true retrocecal specimens.

During the past 10 years, I have encountered 751 instances (25.0 per cent) of acute retrocecal appendicitis among 3,003 consecutive

appendectomies performed for acute appendicitis; the diagnosis was verified by the pathologist in each case. Study of the 751 histories emphasizes the frequently bizarre nature of the early signs and symptoms presented by patients with acute retrocecal appendicitis.

Four hundred and seventy-one (62.72 per cent) of the patients were men. Krasnoselskiy stated the accepted opinion that the incidence of acute appendicitis is less in women, that the condition runs a milder clinical course, and that the mortality is about one third of that occurring in men. Table 2 supports this contention. The average age of the 751

TABLE 2.—*Mortality and Distribution of Diseased Appendixes According to Sex*

Author	Year	Num- ber of Cases	Males				Females			
			Cases		Deaths		Cases		Deaths	
			Num- ber	Per- cent- age	Num- ber	Per- cent- age	Num- ber	Per- cent- age	Num- ber	Per- cent- age
Finney.....	1933	1,807	1,111	61.5	65	5.85	696	38.5	24	3.45
Weyll and Wallace...	1934	8,265	4,652	56.2	241	5.2	3,613	43.8	129	3.6
Lamon.....	1936	206	.....	.....	8	....	.....	.....	6	....
Boyce and others.....	1936	2,715	1,848	68.0	106	5.7	867	32.0	51	5.9
Collins.....	1938	751	471	62.72	41	8.7	280	37.28	17	6.07

TABLE 3.—*Distribution of Diseased Appendixes by Age Group, Expressed in Percentage*

Author	Year	No. of Cases	Age Groups by Years								
			0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	80+
Pattison.....	1936	1,211	10.47	38.3	22.1	10.0	5.78	3.55	1.73	0.33	0.08
Reid and others.....	1936	3,100	6.6	28.3	36.4	18.7	5.78	2.81	1.1	0.29	0.00
Pool.....	1936	757	10.7	41.3	27.7	13.4	4.35	2.11	0.26	0.00	0.00
Rhodes and others..	1936	1,000	8.3	32.7	30.7	13.4	8.3	3.6	1.9	0.3	0.2
		6,068									
Average percentage.....			9.02	35.15	30.97	13.9	6.05	3.02	1.25	0.31	0.14
Collins.....	1938	751	6.25	15.16	40.43	21.55	9.44	4.25	2.13	0.65	0.00

persons was 29.7 years. This age is higher than that usually reported for acute appendicitis. Three hundred and four instances (40.48 per cent) occurred in the third decade of life. There is a noticeable increase in the incidence of this type of appendicitis in the later decades, as depicted in table 3.

Racial and seasonal incidence showed no noteworthy features. The various occupations and previous residences of these persons were unimportant in respect to this study. Interestingly, 267 persons (35.55 per cent) presented histories of other members of their families having suffered attacks of appendicitis that necessitated surgical intervention.

The past histories of these persons were of great importance. Three hundred and one (40.08 per cent) mentioned the previous frequent occurrence of infections of the upper part of the respiratory tract, and in

111 of these (14.78 per cent) such infections had preceded their present acute abdominal complaints by an average interval of 8.4 days. One hundred and thirty-six patients (18.11 per cent) had had recurring attacks of chronic sinusitis of one type or another. Three hundred and seventeen persons (42.21 per cent) still possessed their tonsils or adenoids, and for 293 (38.88 per cent) diagnoses of chronic tonsillitis were recorded in the histories. The most interesting fact in these histories was that 466 persons (62.05 per cent) had had previous similar attacks of abdominal pain of varying degrees of severity. (See table 4 for further details.) One hundred and fifty-one persons (20.11 per cent) had been told in the past by their physicians that they had appendicitis which required immediate surgical intervention. For one reason or another, on receiving this advice, they had failed to permit the performance of surgical abdominal explorations. Of those who had had previous similar attacks of abdominal pain, 113 (15.05 per cent)

TABLE 4.—*Percentage of Patients Having Had Previous Attacks of Appendicitis*

Author	Year	Number of Cases	Previous Attacks	
			Number	Percentage
Merrell.....	1935	2,021	1,200	41.12
Klein.....	1935	86	23	26.7
Reid and others.....	1936	2,035	837	41.12
Pool.....	1936	757	222	27.1
Boyce and others.....	1936	2,715	713	26.3
		8,514		
Average.....	....	....	599	35.2
Collins.....	1938	751	466	62.05

had experienced more than one attack, the average number being 2.4. In the 151 cases, 119 appendixes (15.85 per cent) were gangrenous, 74 (9.85 per cent) had perforated and 13 patients (1.74 per cent) died.

One hundred and thirty-eight persons (18.39 per cent) had been previously treated for cholecystitis of varying severity. Ninety-nine others (13.18 per cent) had been considered in the past as suffering from some form of gastric or duodenal disease. Seventy-one additional patients (9.45 per cent) had received treatment for disease of either the right kidney or the right ureter. Of course, it must be admitted that in all probability some of these persons did actually have such diseases independent of their subsequent attacks of acute retrocecal appendicitis. Sixty-four persons (8.52 per cent) had had cholecystectomies for chronic cholecystitis without cholelithiasis, but had not been relieved of their chief complaints. Fifty-two persons (6.79 per cent) had been operated on for various types of peptic ulcer, without alleviation of their symptoms.



Of the 280 women of this series, 44 (5.86 per cent) had received medical treatment for pelvic inflammatory disease, without obtaining noticeable relief. At the time of the appendectomy, 33 (4.394 per cent) showed no evidence of the previous existence of any pelvic inflammatory disease. Two (0.27 per cent) nephropexies had been performed in the past for conditions in the right side of the abdomen, *without relieving* the patients. Forty-five women (5.99 per cent) had been subjected to various gynecologic procedures, without experiencing permanent relief. An additional 31 (4.13 per cent) had had major pelvic operations of various types, at which, for one reason or another, their appendixes had not been removed.

There were thus 147 persons (19.57 per cent) whose abdomens had been opened previously for other suspected intra-abdominal diseases, but during these operations their appendixes had not been removed, and they subsequently suffered attacks of acute appendicitis. Therefore, most of these persons had been subjected to needless secondary operations, at a time when the operative risk and the postoperative morbidity were greatly increased. Most regrettable was the fact that 6 (0.80 per cent) died. Of the 141 patients (18.77 per cent) with histories of previous abdominal explorations who survived, 131 (92.91 per cent) were relieved of their persistent complaints. Thus, 56.99 per cent of this entire series of 751 patients had received treatment in the past for diseases of the gallbladder, the pyloric region, the pelvis or the right part of the *genitourinary tract*. *Gynecologic operations were the vogue* among the 280 women of this series, while operations on the upper part of the abdomen were fashionable among the 471 men.

Nausea, headache, flatulence, heartburn, regurgitation, insomnia, constipation and lack of appetite, of which many of these patients complained, disappeared in 73.4 per cent of the cases after appendectomies. Distress following the ingestion of cheese, rich or greasy fried foods and raw fruits likewise frequently vanished after the removal of the diseased appendixes. Many persons who complained of symptoms simulating either cholecystitis or peptic ulcer were either cured or greatly relieved after appendectomies. In 12 (1.60 per cent) persons over 55, certain long-continued arthritic pains disappeared after the removal of their appendixes. In 21 persons (2.80 per cent) of the same age group, similar symptoms were greatly diminished by appendectomies, which appreciably increased their usefulness both to themselves and to others.

One hundred and thirty-seven patients (18.24 per cent) complained of mild pains of several days' duration in the epigastric or the right hypochondriac region, which failed to become localized at McBurney's (or more properly, McArthur's) point in the *right lower quadrant* of the abdomen. Two hundred and fourteen persons (28.50 per cent)

complained of steady, dull, deeply situated pains in the right lumbar region of the back. Eighty-eight persons (11.72 per cent) experienced pains in the right shoulder. In 107 instances (14.25 per cent) severe pains in the upper part of the abdomen continued for an average of 6.4 hours. This syndrome was followed by a cessation of the pains and a temporary sense of well-being. However, after the elapse of an average of 4.9 hours, this period of calm was replaced by nausea, vomiting, a feeling of grave illness and diffuse, colicky pains. Only 142 persons (18.91 per cent) presented the fairly classic signs and symptoms of acute appendicitis described in textbooks, and only 2 (0.27 per cent) of this subgroup died of generalized peritonitis.

The average temperature in the mouth at admission was 100.4 F. The pulse rate averaged 88 beats per minute. The average number of respirations was 18 per minute. The average blood pressure per age group, when compared to published normal values, was 30 mm. of mercury less for the systolic and 18 mm. of mercury less for the diastolic reading. The facies and the general appearance of the patients did not usually suggest, on first glance, that they were really sick. One hundred and four persons (13.85 per cent) revealed the existence of either recent or subsiding acute infections of the upper part of the respiratory tract, when the nasopharynx and the lungs were examined. Four hundred and nineteen instances (55.79 per cent) were recorded of the existence of advanced degrees of dental caries or pyorrhea alveolaris. In 57 histories (7.59 per cent), it was recorded that the right side of the diaphragm was limited in its excursion.

The physical examination showed little of interest until the abdomen, back and rectum or pelvis were examined. Inspection of the abdomen usually revealed only the presence of distention in its upper part. Palpation presented a diffuse, mild, generalized tenderness in the right side of the abdomen located lateral and cephalad to McArthur's point. Hyperesthesia of the skin was rarely seen in the right lower quadrant of the abdomen. Muscular rigidity was appreciably less than is usually met with in cases of acute appendicitis and was absent in 397 instances (52.86 per cent). Rebound tenderness was not easily elicited and was absent in 243 cases (32.36 per cent).

The sign most frequently obtained was the production of intense pain by exerting steady, deep pressure on the right flank, lateral to the right psoas major muscle. Percussion was of little value, while auscultation of the abdomen usually gave no remarkable results. In 375 patients (49.93 per cent) the rectal examination gave no sign of tenderness or of a mass in the right side of the pelvis. Yet the rectal examination in 218 instances (29.03 per cent) gave the only positive signs of the existence of acute appendicitis.

The average leukocyte count in this series was 11,870 cells per cubic millimeter of whole blood, with an average differential count of 83.0 per cent of polymorphonuclear neutrophils. Thus, the blood showed a slighter leukocytosis than is usually present in cases of acute appendicitis. Interestingly, the urine of 104 patients (13.85 per cent) contained an appreciable number of erythrocytes, while pyuria was recorded in 152 histories (20.24 per cent), evidence being present in even the catheterized samples. Such urinary observations often were misleading and usually caused operative delay until diagnostic procedures could be utilized to rule out the existence of disease in the right part of the genitourinary system. These patients when operated on later frequently revealed an acutely inflamed appendix lying across the course of the right ureter, with an accompanying secondary acute periureteritis. For 37 women (4.93 per cent) sedimentation rates were determined in an effort to rule out the possible existence of pelvic inflammatory disease. In only 3 instances (0.4 per cent) were the rates abnormal. These observations thus agree with those previously made by Lesser and Goldberger that the sedimentation rate for women suffering from acute appendicitis is normal. (See table 5 for further details.)

Correct preoperative diagnoses of acute appendicitis were made in only 554 cases (73.77 per cent). In the recent study by Rhodes, 75 of his preoperative diagnoses were tabulated as follows: correctness on the question of perforation in 58.6 per cent of the instances, on the question of the location of the appendix in 40.0 per cent and on the question of local pathologic changes in 33.3 per cent. In 136 persons (18.11 per cent) erroneous preoperative diagnoses were made of acute perforated peptic ulcer. In 53 additional persons (7.06 per cent) preoperative diagnoses were made of acute empyema of the gallbladder with impending perforation. Five persons (0.67 per cent) were considered to have acute pancreatitis. Three patients (0.40 per cent) were decided to be suffering from acute mesenteric vascular occlusions.

Of the 554 cases (73.77 per cent) in which correct preoperative diagnoses of acute appendicitis were made, only 304 (40.48 per cent) were correctly diagnosed as of the retrocecal variety. In these 304 cases, as a result of such preoperative diagnoses, 277 (36.88 per cent) lateral and cephalad placed muscle-splitting incisions (rather than the usual McBurney incisions) were made in the right lateral anterior abdominal wall. This type of incision gave an excellent exposure of the retrocecal region and permitted the performance of appendectomy under direct vision, the latter point being a most important factor in lessening postoperative morbidity. (See table 6 for further information.) No herniations occurred postoperatively with this type of muscle-splitting incision. The period of hospitalization of these patients was on

TABLE 5.—*Important Signs and Symptoms Presented in This and Other Series of Cases of Appendicitis*

Signs and Symptoms	Kilnc, 1935	Reid and Others, 1936	Boyce and Others, 1936	Finney, 1933	Collins, 1933
Nausea.....	51.0%	78.0%	.....	.....	56.66%
No nausea.....	.....	.....	2.14%	.....	.....
Vomiting.....	45.0%	73.0%	.....	.....	53.33%
No vomiting.....	.....	.....	2.14%	.....	.....
Constipation.....	31.0%	.....	1.71%	.....	23.46%
Diarrhea.....	.....	.....	.....	.....	13.43%
Pain in right shoulder.....	.....	.....	.....	.....	11.72%
Fever.....	50.0%	.....	.....	.....	63.89%
High fever (102-103 F.).....	.....	.....	4.5%	.....	11.17%
Normal temperature.....	32.0%	.....	20.8%	.....	18.75%
Subnormal temperature.....	16.0%	.....	.....	.....	12.36%
Leukocytosis (over 10,000 cells).....	46.0%	.....	.....	.....	69.43%
White blood count below 10,000.....	.....	.....	17.2%	.....	30.56%
Average leukocyte count.....	.....	17,200	.....	17,660	11,870
Average polymorphonuclear count.....	.....	.....	.....	83.5%	83.0%
Polymorphonuclear count over 80%.....	.....	.....	.....	.....	53.17%
Erythrocytes in urine.....	41.0%	.....	.....	.....	13.53%
Albuminuria.....	9.0%	.....	.....	.....	23.71%
Oasts in urine.....	23.0%	.....	.....	.....	10.11%
Pyuria in catheterized urine specimen.....	12.0%	.....	.....	.....	20.24%
Localized pain in right lower quadrant of abdomen	81.0%	.....	.....	.....	18.88%
Pain elicited in right flank.....	.....	.....	.....	.....	63.31%
Muscular spasm localized in right lower quadrant	.....	.....	.....	.....	.....
of abdomen.....	52.0%	.....	.....	.....	47.20%
Limited excursion of right side of diaphragm.....	.....	.....	.....	.....	7.59%
Boardlike muscular rigidity.....	10.0%	.....	.....	.....	4.52%
Sedimentation rate abnormal.....	.....	.....	.....	.....	8.11%
Use of Penrose drains.....	42.0%	.....	.....	.....	31.84%
Rebound abdominal tenderness.....	35.0%	.....	.....	.....	67.64%
Abdominal pain.....	.....	91.0%	96.3%	.....	83.12%
Rectal tenderness.....	.....	44.0%	.....	.....	50.07%
Typical history of appendicitis.....	.....	53.0%	.....	.....	18.91%
Average temperature.....	.....	100.1 F.	.....	.....	100.4 F.
Average pulse rate.....	.....	89	.....	.....	88
Typical history of pelvic disease.....	.....	.....	0.59%	.....	6.62%
Typical history of perforated peptic ulcer.....	.....	.....	.....	.....	18.11%
Typical history of cholecystitis.....	.....	.....	0.44%	.....	7.06%
Typical history of renal disease.....	.....	.....	0.07%	.....	11.17%
Typical history of ectopic pregnancy.....	.....	.....	0.07%	.....	0.00%
Association with respiratory disease.....	.....	.....	7.53%	.....	13.85%
Association with.....	.....	.....	1.43%	.....	9.57%
Association with.....	.....	.....	3.03%	.....	16.49%
Pain in left side of abdomen only.....	.....	.....	0.73%	.....	1.19%
No localization of pain in right lower quadrant of	.....	.....	.....	.....	.....
abdomen.....	.....	.....	2.23%	.....	18.24%
Advanced dental caries, pyorrhea.....	.....	.....	.....	.....	55.79%

TABLE 6.—*Incidence of Postoperative Complications in Reference to Type of Incision Used*

	Type of Incision			Totals
	Muscle-Splitting	Midright Rectus	Midline	
Number of cases.....	277	313	161	751
Postoperative complications				
Postoperative morbidity.....	77 (10.25%)	178 (23.70%)	141 (18.75%)	396 (52.73%)
Pelvic.....	24 (3.20%)	31 (4.13%)	42 (5.59%)	97 (12.92%)
Second.....	0 (0.00%)	10 (1.33%)	21 (2.80%)	31 (4.13%)
Hernias after incision.....	0 (0.00%)	17 (2.26%)	34 (4.53%)	51 (6.79%)
Average number of days in the hospital....	16	23	27	
Average time spent at performing operation.....	37 min.	51 min.	62 min.	
Sex: Males.....	251 (33.42%)	172 (22.90%)	48 (6.39%)	471 (62.72%)
Females.....	26 (3.46%)	99 (13.18%)	153 (20.64%)	280 (37.28%)
All deaths.....	12 (1.60%)	18 (2.40%)	28 (3.73%)	58 (7.72%)

an average 9 days shorter and only one-eighth as many postoperative complications occurred among them as among those having had either midright rectus or midline incisions. Consult table 6.

However, in instances in which a doubt existed as to the cause of the acute condition in the abdomen, preliminary exploratory midright rectus incisions were made at the level of the umbilicus, so that they could be extended either caudally or cephalically as the intra-abdominal observations dictated. In 77 patients (10.25 per cent) walled-off retrocecal abscesses were palpated through such exploratory incisions. These

TABLE 7—*Tabulation of Postoperative Complications in This and Other Series of Cases of Acute Appendicitis*

Postoperative Complications	Author and Number of Cases Reported				
	Boland, 4,270	Weyll and Wallace, 8,265	Pattison, 1,148	Sperling and Myrick, 433	Collins, 751
Ileus	33				23
Fecal fistula	7	59			2
Enterostomy	18	50	9		6
Bronchitis		150			59
Bronchopneumonia	12	19	7		8
Lobar pneumonia	0	46			10
Pulmonary atelectasis		13			19
Pulmonary embolism	2	8			0
Empyema	1	8			4
Cardiac disease	3				19
Peritonitis	335	1,274	120	68	161
Pleurisy		18			22
Lung abscess		1			6
Infected incision		234	67	22	95
Incomplete intestinal obstruction		56			14
Acute intestinal obstruction		67	9	5	22
Peritonitis with obstruction		22			9
Subdiaphragmatic abscess		17	2		11
Subhepatic abscess			2		7
Thrombosis and phlebitis		32			26
Pelvic abscess		30	41		97
Intra abdominal abscess		23	11		51
Appendical abscess	197	1,123	268	107	254

were then closed without disturbing the abscesses and secondary muscle-splitting incisions were made directly over the abscesses and proper drainage instituted.

In the remaining 474 cases (63.12 per cent), in which either midright rectus incisions (313—[41.68 per cent]) or midline incisions (161—[21.44 per cent]) were employed, the appendixes were removed usually through lengthened incisions with considerable difficulty. This necessitated increased retraction of the edges of the wound, with a resultant increased degree of trauma to the anterior abdominal wall. Thirty-one (4.12 per cent) such incisions required a secondary closure before the patients could be dismissed from the hospital. In 51 additional cases (6.79 per cent) hernias of varying degree developed after incision. There were 319 examples (42.48 per cent) of troublesome complications.

that developed in the non-muscle-splitting incisions. (Consult table 6 for further details.) The average stay in the hospital for patients with incisions of this type was 25 days, as compared to 16 days for those with muscle-splitting incisions.

Localized abscesses were drained by the use of simple Penrose drains of soft rubber dam material. These drains were completely removed

TABLE 8.—*Average Number of Days Spent in the Hospital According to the Pathologic Condition Found*

Author	Year	Number of Cases	Simple Acute Appendicitis	Appendicitis with Abscess	Appendicitis with Generalized Peritonitis
Finney.....	1933	3,913	14.3	23.8	34.7
Merrell.....	1935	2,921	S.S.	....	27.3
Reid and others.....	1936	2,921	8.21	....	27.3
Sperling and Myrick....	1937	433	9.75	22.0	23.0
Collins.....	1938	751	16.0	21.5	26.0

TABLE 9.—*Mortality in Relation to Type of Appendicitis*

Type of Appendicitis	Number of Cases	Percentage of 751	Number of Deaths	Percentage of 751	Percentage of Type	Mortality Due to Appendicitis
Acute simple appendicitis.....	154	20.50	1	0.133	0.65	0.000%
Nonperforated gangrenous appendicitis..	202	26.90	10	1.332	4.95	1.064%
Appendicitis with abscess or localized peritonitis.....	234	31.16	15	1.997	6.41	1.862%
Acute appendicitis with perforated appendix and general peritonitis.....	161	21.44	32	4.261	19.88	3.451%
Totals.....	751	100.00	58	7.723		6.407%

TABLE 10.—*Causes of Death in This Series*

Condition	Number of Cases	Number of Deaths	Percentage of 751	Percentage of Condition
Pelvic abscess.....	97	12	1.60	12.37
Subdiaphragmatic abscess.....	11	4	0.53	36.36
Liver abscess and ascending pyelophlebitis.	8	8	1.06	100.00
Pneumonia.....	68	9	1.20	13.24
Generalized peritonitis.....	113	25	3.33	22.12
Totals.....	207	58	7.72	

by the twelfth day after operation. Drainage was not instituted in instances of generalized peritonitis, the peritoneum being tightly closed. However, the layers of the incision were only loosely closed, and dependent drainage down to the peritoneum or rectus muscle was instituted. There were 97 examples (12.92 per cent) of secondarily formed pelvic abscesses that required drainage. Seventy-three (9.72 per cent) of these pelvic abscesses occurred in persons whose operations were performed through either midright rectus incisions or midline incisions.

Twelve (1.60 per cent) of the 97 patients with pelvic abscesses died; 10 (1.33 per cent) of these deaths were attributable to the non-muscle-splitting incisions. These pelvic abscesses, after their localization, were

TABLE 11.—*Percentage of Mortality per Age Group Compared With Previously Reported Series*

Age Groups (in Years)	Percentage of Mortality per Age Group	
	Average of 21,289 Cases Reported by Various Authors* Between the Years of 1931-1936	Collins, 1938, 751 Cases
1-10.....	10.6	10.8
11-20.....	2.66	4.3
21-30.....	4.0	4.3
31-40.....	6.7	4.9
41-50.....	11.14	14.1
51-60.....	11.70	23.0
61-70.....	21.65	50.0
71-80.....	57.2	40.0
81-90.....	100.0	....

\* Bower (in 1931); Wevill and Wallace; Pattison; Pool; Boyce and McFetridge, and Rhodes, Birnbaum and Brown.

TABLE 12.—*Relationship of Duration of Symptoms Before Operation With Percentage of Mortality in Acute Appendicitis; Comparison of This Series With Others*

Time in Hours	Author, Year and Number of Cases Reported					
	Bower, 1931, 5,121	Boland, 1932, 4,270	Maes and Others, 1933, 2,295	Pattison, 1936, 1,166	Boyce and Others, 1936, 2,715	Collins, 1938, 751
0-6.....	2.35	0.00	2.0	0.00	1.6	1.7
7-12.....		1.00				0.0
13-24.....		2.32		0.48	2.8	3.5
25-48.....	6.31	6.45	4.6	5.60	4.8	5.9
49-72.....	8.59	6.50	7.5		6.8	7.3
Over 72.....	11.83	8.00	12.3	9.80	15.7	13.2

TABLE 13.—*Mortality for the Surgical Treatment of Acute Appendicitis*

Author and Year	Total Cases	Total Deaths	Average Mortality, Percentage
Various authors,* 1931 to 1937.....	60,130	3,046	5.06
Collins, 1938.....	751	35	7.714

\* Bower; Boland; Finney; Keres; Reid; Wevill and Wallace; Stanton; Harris; Cayford; Lied; Black; Merrell; Kilne; Eiken; Maes and McFetridge; Krasvoselskiy; Greiner; Schroder and Steinel; Lamon; Liveland; Hobler; Reid; Poer and Merrell; Nuzum; Pattison; Cook and Beardsley; Pool; Boyce and McFetridge; Rhodes, Birnbaum and Brown; Jensenius; Sperrling and Myrick, and Holder and Wells.

drained, wherever possible, either through the anterior rectal wall in men or through Douglas' cul-de-sac in women. No permanent fistulas resulted from such methods of drainage, and none of the patients died.

Eleven instances (1.46 per cent) of subdiaphragmatic abscesses were encountered and 4 of the patients affected died. There were 8 patients

(1.07 per cent) with multiple abscesses of the liver, all of whom died. Of 69 persons (9.19 per cent) with postoperative pneumonia, 9 (1.20 per cent) succumbed. Twenty-seven (3.6 per cent) of this group had had definite preoperative infections of the upper part of the respiratory tract. Among the 113 instances (15.05 per cent) of generalized peritonitis, there were 25 deaths (3.33 per cent).

TABLE 14.—*Mortality in Relation to Types of Abdominal Incision*

Authors	Year	Number of Cases	Paramedian and Midright Rectus	Muscle-Splitting and McBurney's
Taylor	1935	110	40.00	10.00
	1936	2,035	9.50	5.40
	1936	1,181	6.4	0.6
Collins.....	1938	751	6.12	1.60

TABLE 15.—*Mortality in Various Types of Acute Appendicitis; Comparison With Other Series Reported in the Literature*

Author and Year	Total Cases	Average Incidence in Percentage		
		Acute Appendicitis with Nonperforated Appendix, Including Gangrenous Specimens	Acute Appendicitis, with Perforated Appendix, Abscess or Local Peritonitis	Acute Appendicitis, General Peritonitis
Various authors,* 1933 to 1937....	18,899	1.45	6.24	23.57
Collins, 1938.....	751	3.09	6.41	22.12

\* Finney; Keyes; Harris; Cayford; Haggard; Jeld; Merrell; Elken; Reid; Poer and Merrell; Lamon; Hobler; Pattison; Rhodes, Birnbaum and Brown, and Sperling and Myrick.

TABLE 16.—*Deaths Caused by Preoperative Catharsis; Comparison With Other Series*

Author and Year	Number of Cases	Average Percentage of Patients Having Had Laxatives	
		Among Total Postoperative Deaths	In Entire Series
Various authors,* 1931 to 1937.....	21,296	47.4	29.1
Collins, 1937.....	751	50.0 (29 cases)	18.2 (137 patients)

\* Bower; Boland; Keyes; Merrell; Lamon; Reid, Poer and Merrell; Cook and Beardsley; Boyce and McFetridge, and Sperling and Myrick.

Thus, in the entire series of 751 cases, there were 58 deaths (7.72 per cent), as detailed in tables 9 to 13. However, only 12 (1.60 per cent) of the total of 58 deaths occurred in the cases in which muscle-splitting incisions were performed. (Consult table 15 for additional data.) Twenty-nine (3.86 per cent) of the 58 patients who died had taken one or more doses of laxative prior to entrance into the hospital. (See table 16 for further details.) This fact fully substantiates the



previous contentions of Bower as to the deadliness of preoperative catharsis in instances of acute appendicitis.

Some of the important features of the operative technic were briefly as follows: Less attention was paid to the day of the disease than to the condition of the patient. If the patient was growing steadily worse, exploration was usually believed to be indicated. If, on the other hand, the patient had a palpable mass in the lower part of the abdomen and was improving, surgical intervention was not employed at that time. Spinal anesthesia was used routinely unless some condition was present in the patient that served as a definite contraindication to its use. Every possible effort was made to drain extraperitoneally localized appendical abscesses, but such abscesses were never drained across the clean peritoneal cavity. Only localized appendical abscesses were drained by the use of simple Penrose drains constructed from rubber dam material.

If the appendix formed part of the wall of an abscess, if its removal would lead to the extensive breaking down of protective adhesions or if the patient was a poor risk, operative time was not wasted, nor was the life of the patient placed in additional jeopardy by foolish insistence on the completion of a difficult appendectomy. In such cases the patients were asked to return to the hospital for the performance of an interval appendectomy 10 weeks after their dismissal. All pelvic abscesses were drained, if possible, through either Douglas' cul-de-sac or the anterior rectal wall. The stump of the appendix was not inverted, and no reason has been encountered to regret the use of this simpler technic. I employ muscle-splitting incisions as a matter of routine whenever possible, because I believe that the use of such incisions insures a definite lowering of both the operative mortality and the postoperative morbidity. In no instance was a tight reapproximation of the edges of the skin permitted. Skin clips were used by preference. At the first sign of infection of the wound, adequate through and through drainage was instituted, both to hasten the final healing of the incision and to prevent the onset of extensive phlegmons of the anterior abdominal wall, which are often of anaerobic origin.

All patients were placed in Fowler's position postoperatively, and the principles of Ochsner were closely followed. Nothing was given by mouth until flatus was passed, abdominal distention had disappeared and the temperature had fallen toward normal. In the interim, fluids were usually administered by hypodermoclysis, or, if necessary, by the intravenous route, usually in daily amounts of 2,000 cc. No patient was allowed to be out of bed until the incision was healed and the temperature had been afebrile for 4 days. Before dismissal from the hospital, a rectal examination was mandatory to exclude the possibility of the

presence of a silent secondary pelvic abscess. All patients were closely followed for a month after dismissal from the hospital, and after that at less frequent intervals.

### CONCLUSIONS

Seven hundred and fifty-one instances of acute retrocecal appendicitis have been reported. The mortality for this series was 7.72 per cent. Comparisons between acute retrocecal appendicitis and the ordinary acute types reported in other series lead one to the conclusion that this is the most dangerous form of appendicitis. Data from this material showed that muscle-splitting incisions are the safest and that they constitute a significant factor in the reduction of both the operative mortality and the postoperative morbidity.

Women appear to withstand the ravages of appendicitis better than men. The deadliness of preoperative self catharsis has been again substantiated. Appendixes assume a fixed retrocecal position from adhesions produced by previous attacks of acute appendicitis. Sixty-two per cent of the patients of this series had had previous similar attacks. The mortality appreciably increased in the first and after the fifth decade of life. Forty-three per cent of the total deaths were due to generalized peritonitis. Fifty per cent of those who died had had preoperative self catharsis. A plea is earnestly made for the recognition of this dangerous and atypical variety of appendicitis.

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# FRESH FRACTURE OF THE OS CALCIS

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A broken leg as a rule causes too great a disability to allow a mistaken diagnosis. Not so with many fresh fractures of the os calcis. If the damage is severe enough the physician's attention is focused and his diagnostic curiosity challenged to the point that early roentgenograms are generally taken. Thus, a "sprain" turns out to be a crushing fracture of the heel bone. Too often, even in the larger centers, the ancient empirical form of treatment, consisting of "rest in an encasement until consolidation has arrived," is applied. I wish to advocate, briefly, a manner of treating fresh fracture of the os calcis by closed reduction, modeling the fragments by force and encasing the restored foot until healing takes place.

## HISTORICAL TREATMENT

In 1720 Garangeot, of France, first described accurately the "smash fracture." Petit and Desault, his countrymen, reported their cases in the same year and advised "rest until fragments had consolidated." Bilgner, of Germany, in 1720 added to the literature a good clinical description of the injury. For one hundred years no one propounded any change in the treatment, though a number of papers were published. The surgeon of that time appeared contented to describe in great detail every clinical variation of the condition and was not much interested in treatment. Cooper, in England, in 1835 recommended dressings of egg albumin and cotton lint unless the extremity appeared gangrenous; if it was gangrenous he amputated. Pott sawed off the ends of the bone in all cases of compound fracture to prevent tetanus and so, of course, sawed away the heel bone when it was badly damaged. Mutilation and frequent deaths followed, as may be imagined. In 1839 Norris, the first American to report his results, followed the same rugged form of treatment. The first classic description and discussion of the mechanics involved in the production of this type of fracture were written by Nadal and Malgaigne in 1843, in Paris. Bérard in 1845, Bauchet in 1853 and Demarquay in 1854 advised the use of lint and cottage cheese encasement.

Clark, an American, in 1855 applied traction to the posterior fragment by means of a pulley apparatus; the exact method is not clear from his writings. He then used gutta-percha splints. Every one feared the

open approach to reduction until Charles Bell, of Edinburgh, in 1882 made it an accomplished fact in the case of a compound fracture. After reduction a lint packing treated with phenol was instilled into the wound, with "rest until consolidation took place" completing the treatment. Paszkowski in 1880 used the first encasement of plaster of paris. Bailey, of Oregon, in one of the first American medical journals, recommended "elevation, lotions, saline cathartics and no splints." He added that the foot is always stiff as an end result. The laborer's compensation laws of Europe, developed at about this time, caused an increased interest in fractures, and fracture of the os calcis came in for its share. German surgeons provided most interesting contributions.

The greatest incentive for better methods of treatment came with the advent of the roentgen ray, in 1895. Desfosses reported the first roentgen study of fracture of the os calcis and described the tearing so often found at the attachment of the achilles tendon. Helbing, Neuschafer and Lemmen in 1900 manually manipulated the foot over a wooden wedge and then encased it in plaster. Lecocq, of Lille, used relaxing massage with the knee flexed. Gérard, of Paris, in 1902 reported the use of fixation by means of bands of plaster of lead oleate and silver wire. Most authorities advised early weight bearing, with daily massage and exercise.

All this work occurred "B.C.," before Cotton, who in 1908 first published his method, used more universally thereafter than any other. Cotton and Wilson described their method of breaking up impaction of fragments and reduction by means of molding manually, after traction of the posterior portion of the body had pulled down the rear fragment. Impaction was accomplished by means of a sharp blow with a mallet over a felt pad, directed against the point of the heel. Traction was accomplished by means of a steel sound passed behind the achilles tendon and over the calcaneum. Motion in the subastragalar point was made certain by manually moving the lower part of the foot laterally and then applying a plaster encasement. Years later Cotton modified the traction method by using ice tongs and weight traction, with the foot and leg in a Thomas splint when the fracture was stubborn. Pads were strategically placed beneath each malleolus for pressure, and the foot was turned up in plantar flexion with inversion. The encasement was removed in four weeks, and weight bearing was allowed, with a transverse arch pad in the shoe. Cotton has changed recently to more conservative ways, not allowing weight bearing before the eighth or tenth week.

Curiously, in 1933, in discussing fracture of the os calcis in one of the leading surgical systems, Cotton stated that nothing was done about treatment until 1907-1908. American surgeons regarded Cotton's method highly, and many reported their results with it. A number

modified the method by substituting tenotomy of the achilles tendon. Cotton in 1921, in another classic, using freehand drawings from his notebook, a form of illustration which always enlivens an otherwise staid manuscript, expressed the opinion that impaction is not altogether sound mechanically and directed attention toward the remodeling of fragments as perhaps the most important step. He said that in all cases arthrodesis is distinctly inadvisable and that he preferred to break up adhesions in the subastragalar joint and restore lateral mobility. He then permitted weight bearing after the eighth week.

The following outline, illustrated in figures 1 and 2, is a review of the manifold ways of treating fractures of the os calcis.

## 1905

Eisendrath: open reduction, fixation with kangaroo tendon, cast.

## 1908

Cotton and Wilson: closed reduction after breaking up of impaction with a mallet, traction on the achilles tendon, reimpaction, cast with felt pads beneath malleoli for compression and under longitudinal arch of foot.

## 1912

Van Stockum: open reduction with subastragalar arthrodesis, cast.

## 1913

Drewke: open reduction, cast.

Gelinsky: closed reduction, drill fixation from without, cast.

Leriche: open reduction, bone plates, steel screws for fixation, cast.

Soubeyran and Rives: primary astragalectomy.

## 1916

Lounsbury: Cotton's technic, occasionally open reduction, fixation with kangaroo tendon, tenotomy, cast.

Forrester: manual manipulation, tenotomy, cast (with the foot in plantar flexion over a roller bandage and the heel well down), fixation with kangaroo tendon if necessary.

## 1917

Bendixen: Cotton's technic, carpenter's clamp or fixation with kangaroo tendon, cast.

Cahill: Cotton's technic or fixation with nail, cast.

Magnuson: essentially Cotton's technic plus tenotomy, cast, then special shoe.

## 1918

Whiteside: open reduction, fixation with silver wire, tenotomy, cast.

## 1919

Davis: Cotton's technic.

## 1920

Foldes: Fischer's leaf spring apparatus for external traction for reduction and maintenance, pin through posterior fragment.

Mumford: essentially Cotton's technic, with reduction leverage over iron pipe and tenotomy.

Magnuson: former technic plus reduction leverage over wedge, cast, weight bearing in eight weeks.

## 1921

Beedle: gradual reduction by daily manipulations, followed by use of a cast.

Straus: Steinman pin through posterior fragment, traction and reduction on Hawley table, cast.

Moreau: subastragalar arthrodesis immediately, occasionally astragalectomy and once amputation of foot.

Magnuson: old fractures, new bed for peroneal tendons, wrenching of foot, cast, Thomas heel and felt arch support in shoe.

Cotton: former technic plus cast with pad beneath lateral malleolus.

## 1922

Kaess: two pin traction on posterior fragment in plaster boot, heel portion fenestrated.

## 1923

Becker: open reduction by forcible leverage, fixation by drill point, cast over all.

## 1924

Sneed: Cotton's technic plus tenotomy, occasionally removal of excess bone beneath lateral malleolus, with subastragalar arthrodesis (old fractures).

Elsner: closed reduction, fixation with nail, cast.

## 1925

Hall: essentially Cotton's technic plus tenotomy.

## 1926

Harding: cabinet maker's D clamp to reduce and mold fragments, traction by claw retractor buried above os calcis, all over wedge in sole of foot, cast, weight bearing after twelve weeks.

Brickner and Milch: essentially Cotton's technic plus walking iron in cast and early bivalving, with active motion and massage.

Conn: direct traction, tenotomy, cast, occasionally subastragalar arthrodesis.

Condit: Cotton's technic plus tenotomy.

Reich: triple arthrodesis (old fractures), cast for twelve weeks.

## 1927

Speed: open reduction, fixation with catgut or ivory peg, general preference for Cotton's technic for closed reductions.

Funsten: Cotton's technic plus tenotomy.

Wilson: open reduction plus subastragalar arthrodesis, cast.

## 1928

Masland: cast to ankle, cast over forepart of foot, then iron clamps to compress and reduce fractures, plus pads under joining of cast.

Glasson: Cotton's technic.

Bendixen: Cotton's technic plus tenotomy.

Lenormant, Wilmoth and Lecœur: open reduction, with elevation of astragalus, plus osteoperiosteal grafts from lateral malleolus to fill defect in os calcis, cast.

## 1929

Böhler: closed reduction, wooden wedge in sole of foot to break up impaction, heel forced down, iron clamp for compression, pin through tibia and pin through posterior fragment of os calcis, knee flexed 90 degrees in frame stirrup, counter-traction on tibia, traction on os calcis, first cast for from three to five weeks, second cast for from nine to fourteen weeks, with walking iron, arch support in shoe.



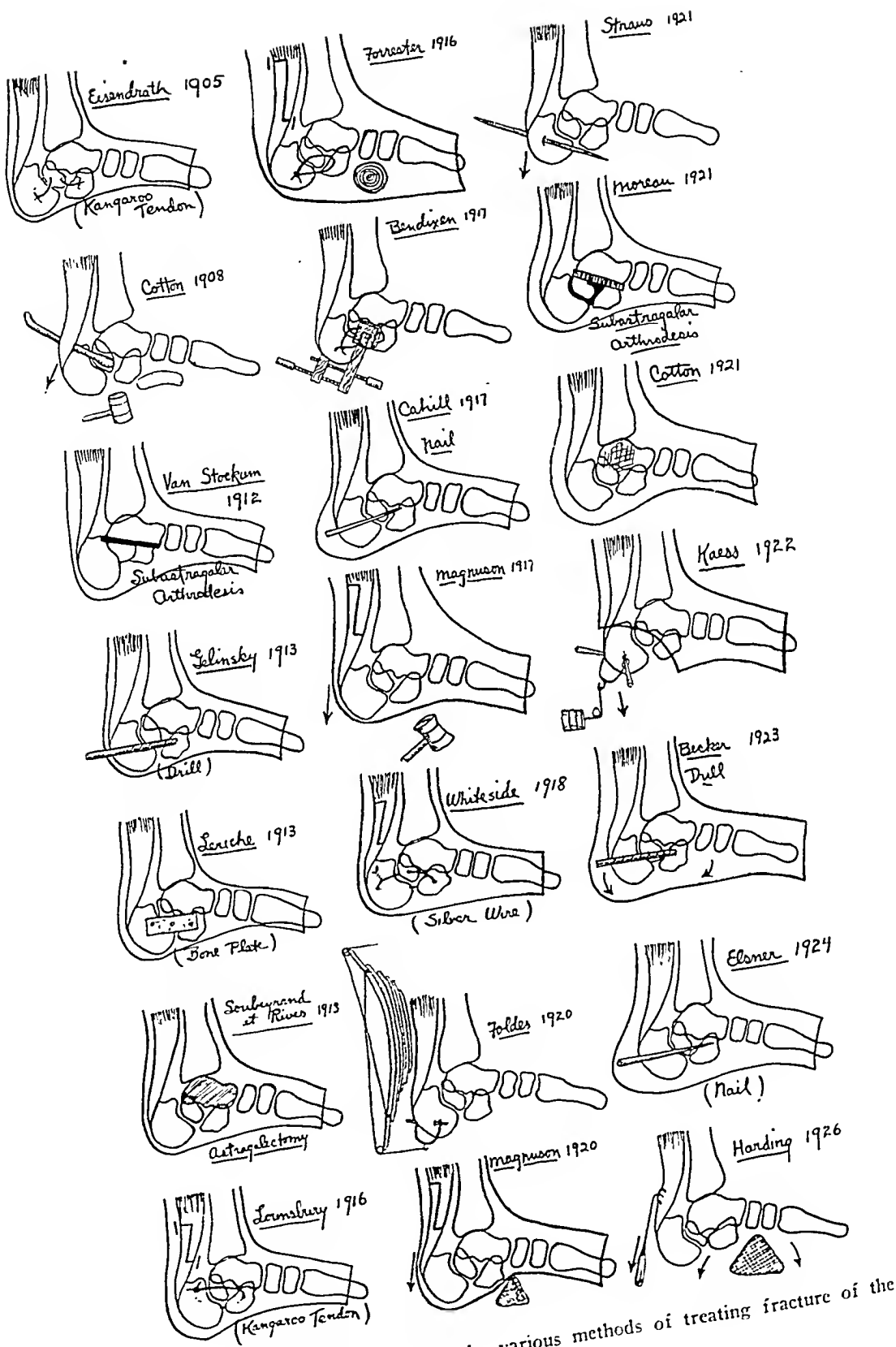


Fig. 1.—Pictorial review of the various methods of treating fracture of the os calcis.

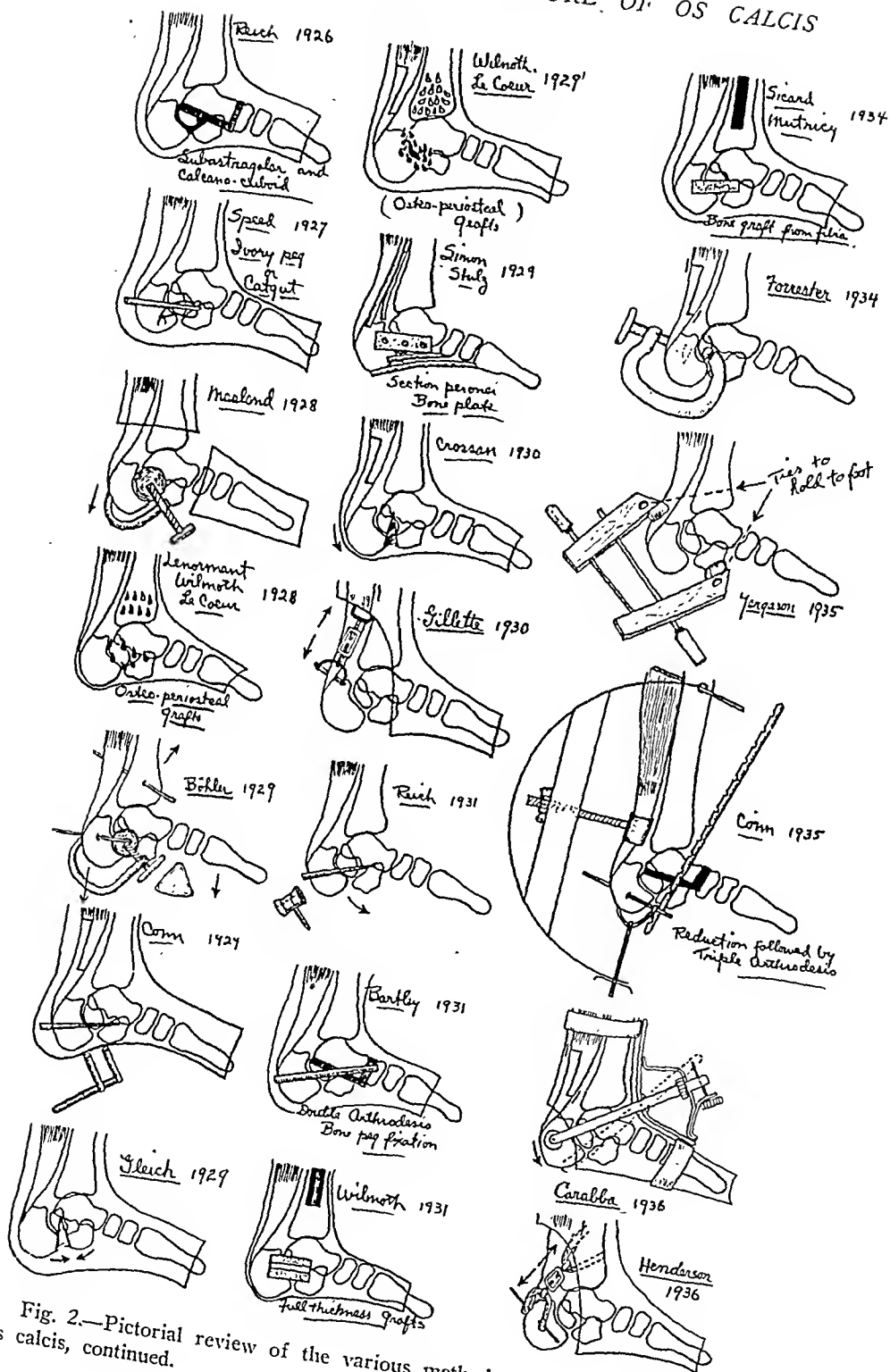


Fig. 2.—Pictorial review of the various methods of treating fracture of the os calcis, continued.

Conn: closed reduction, wrenching of foot, tenotomy, fixation with nail, cast, occasionally subastragalar arthrodesis.

Gleich: open reduction, wedge osteotomy, cast (fresh fractures).

Bérard and Mallet-Guy: open reduction, cast.

Schnek: Böhler's technic.

Wilmoth and Lecœur: open reduction, osteoperiosteal grafts, no cast for first week, then cast for twelve weeks.

Chatterton: Cotton's technic, with tenotomy.

Oudard and Le Bourgo: closed reduction by hand, cast, occasionally open reduction with fixative material and subastragalar arthrodesis.

Simon and Stulz: open reduction, sectioning of peroneal tendons, fixation with bone plate, suture tendons, cast; sequestration frequent result.

Schwartz: open reduction, cast.

Fontoynt and Estrade: cast alone.

### 1930

Bendixen: carpenter's clamp, with two blocks for compression, plus Cotton's technic, occasionally open reduction, fixation with kangaroo tendon, cast.

Crossan: triple arthrodesis, wedge osteotomy, tenotomy, cast (old fractures).

Simon and Stulz: open reduction, subastragalar arthrodesis, with packing in of bits of fragments cut from fracture site or medial malleolus (inner incisional approach), occasionally use of bone plates, screws.

Gillette: cast from toes to groin, fenestrated heel portion, turnbuckle component embedded in cast for push on pin above os calcis, behind achilles tendon, to accomplish reduction and fixation.

Pichon: open reduction, with osteoperiosteal grafts, cast.

Dieulafe: open reduction, fixation with silver wire, cast.

Hermann: Cotton's technic.

Dachtler: special fracture, cast alone.

### 1931

Reich: traction on heel plus impaction with mallet, occasionally fixation with nail, cast.

Bartley: open reduction, double arthrodesis, fixation with bone peg, cast.

White: rapid Böhler technic with patient on Hawley table, reduction accomplished immediately, cast wedged for further correction if necessary.

Mouchet and Allard: cast alone.

Didiée: fracture of apophysis, rare, manual replacement, cast.

Monod: cast for four weeks, then double arthrodesis.

Patel, open reduction, fixation with nail, cast, spontaneous arthrodesis desired.

Wilmoth: open reduction, grafts with full thickness from shaft of tibia for fixation, cast.

Böhler: former technic.

### 1932

Harding: former technic, occasionally fixation with screw or nail.

Reich: Cotton-Funsten combination, occasionally plus Böhler's technic.

Mouchet, Allard and Mégnin: special fracture of anterior portion of large apophysis, cast alone, with foot in marked dorsiflexion.

### 1933

Pierce: Cotton's technic, occasionally subastragalar arthrodesis.

Myers: impaction allowed to remain, cast for only three weeks, early weight bearing.

Funsten: compression bandage one week with elevation, Cotton's technic plus tenotomy, Thomas brace for early walking.

Moore: special fracture of tuber calcanei, rubber ball in cast under heel for pressure, cast for three weeks.

## 1934

Westhues: closed reduction, fixation with nail, cast for three weeks.

Sicard and Mutricy: open reduction, bone graft full thickness from tibia, tenotomy, cast after fifteenth postoperative day to permit swelling to subside.

Stewart: elevation, ice, closed reduction, cast, occasionally Böhler's technic, subastragalar arthrodesis if other methods failed.

Forrester: closed reduction, iron clamp for compression, tenotomy, walking iron incorporated in molded plaster splints.

Oscrow: Wilmoth's technic.

Laffitte: open reduction, essentially the technic of Sicard and Mutricy.

## 1935

Yergason: closed reduction, molding of fragments with powerful clamp, special blocks on jaws, cast with walking irons.

Conn: modification of Böhler's technic, with extremity in a rocking apparatus, plus triple arthrodesis.

Mutricy: former technic preferred.

## 1936

Schofield: Böhler's technic.

Carabba: reduction device with pin through posterior portion; cast cut out around posterior portion, arm of device moves through arc and pushes down posterior fragment, cast then holds reduction by incorporating pin, pin unscrews in midportion for removal.

MacAusland: Böhler's technic.

Henderson: Modification of Gillette's technic, with cast; traction on posterior portion, with pin and turnbuckle incorporated in cast.

## PROGNOSIS

Every one is agreed that fracture of the os calcis is the most disabling of all fractures involving the bones of the leg or the foot. Mercer said that it is the most disabling of all injuries. He stated that the injured person never completely recovers movements of inversion and eversion if the fracture involves the subtaloid joint. He gave as a prognosis from three to four years before complete recovery. Kessler suggested from three to four months of disability for minor fractures and from eight to twelve months for severe types. He did not hazard a statement of the usual percentage allowed for permanent partial disability in settled cases.

Harding gave five months for the average period of disability. Hermann reported 77 per cent of good results. Funsten allowed a period of disability of just under six months. Böhler did not come down to actual figures, but said that this fracture is a very disabling one. Forrester stated that the average period of disability for his patients was four and one-half months, with an average ultimate specific loss of 18

per cent. The general trend appears to be in the direction of less time lost from employment and much lower percentage allowances for permanent partial disability, in spite of a contrary opinion held by most insurance carriers.

#### TREATMENT

Eight patients with fresh fracture of the os calcis were treated by immediate reduction, with gas-oxygen anesthesia and a modified carpenter's clamp described by Yergason in 1935 being used. Such a clamp can be adapted for this use by fastening to the inner surface of each jaw, near the tips, a rounded wooden block about 4 cm. in diameter.

The blocks attached to the inner surface of each jaw are applied over thin felt to the lateral and the medial sides of the heel, and the clamp is screwed down by compression. One exerts tremendous force on the

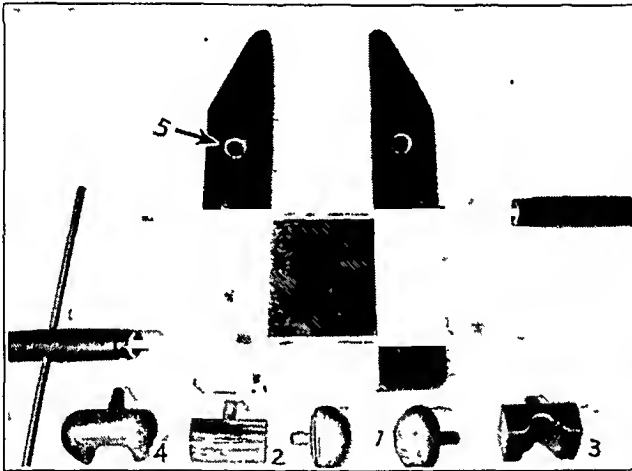


Fig. 3.—Clamp used in molding the fragments and reducing the fracture. 1, hemispherical blocks for lateral modeling; 2, oblong block used against plantar surface; 3, grooved block to fit around the attachment of the achilles tendon over the tuberosity; 4, semilunar block used beneath the lateral malleolus, and 5, holes through the jaws to carry muslin ties to hold the clamp to the foot.

fragments in this manner, loosening the clamp and shifting its jaws over the surfaces to compress and mold the heel. A crescent-shaped block, easily made in one's workshop, is then substituted for one of the rounded blocks, and the extruded fragments are pressed into the body of the os calcis by applying the jaw bearing this crescent-shaped block beneath the lateral malleolus. In this manner all medial and lateral displacements can be corrected by pressure modeling with surprisingly little difficulty.

In cases of evulsion of the upper tuberosity, or fish mouth fracture, in which a fragment is pulled upward by the achilles tendon and there is plantar displacement of other fragments, the bones are molded forcibly

into position by applying the clamp at a right angle to the first position described. The crescent-shaped block on one jaw is placed over the attachment of the achilles tendon, and a square block, with edges smoothed, attached to the other jaw is applied on the plantar surface

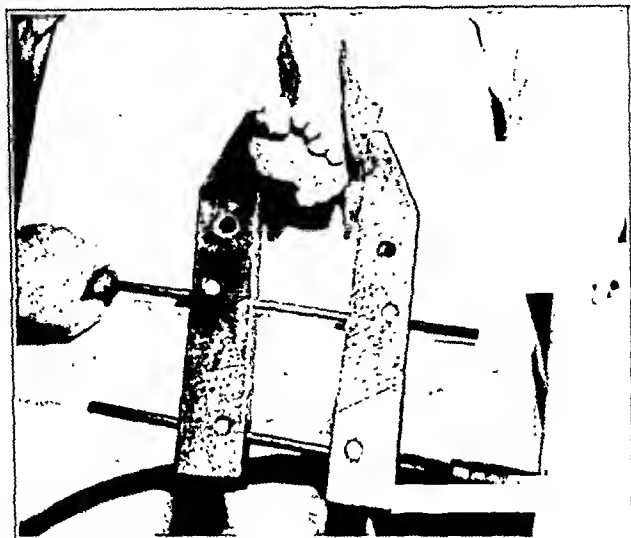


Fig. 4.—First position of application of force, with two hemispherical blocks, or jaws.

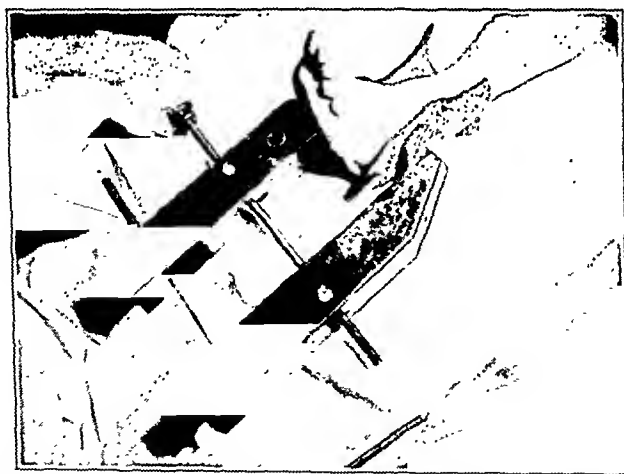


Fig. 5.—Second position, in which one hemispherical block and the semilunar block compress the fragment beneath the lateral malleolus that might extrude.

over the head of the os calcis. The clamp is then snugly adjusted while an assistant ties each jaw to the foot with a muslin loop passed around the foot, above and below the malleoli and through a hole in each jaw. These ties prevent the heel from sliding out of the clamp when the handles are screwed down and the jaws compressed. Thin felt must

always be used beneath the blocks and the muslin ties. The displaced fragments are then forced into position, and the posterior part of the os calcis is brought into normal relations with the head, so that the normal tuber joint angle is restored. This angle, described by Böhler, is made by the intersecting of a line drawn from the posterior-superior tuberosity of the os calcis to the superior-posterior portion of the astragalocalcaneal joint and a line drawn from the superior-posterior portion of the astragalocalcaneal joint and the anterior-superior projection of the head of the os calcis. This angle is normally between 25 and 35 degrees. Thus a tenotomy of the achilles tendon is unnecessary for reduction of the upper posterior fragment. This type of clamp is superior to Böhler's clamp because it permits application of much

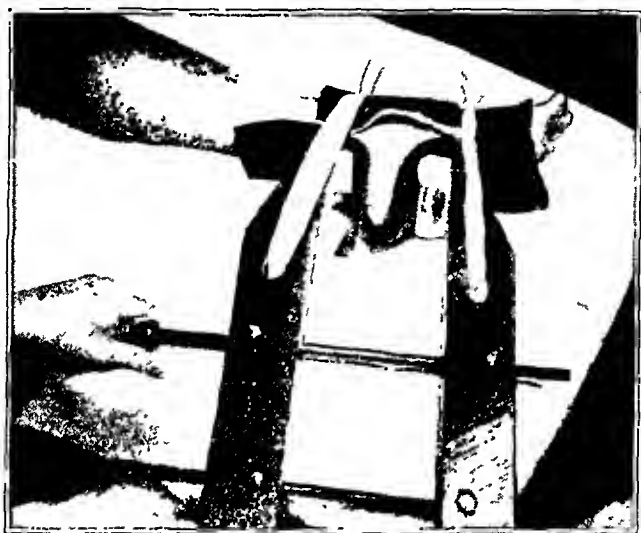


Fig. 6.—Third position, in which blocks 2 and 3 are used to bring down the posterior tuberosity and raise the head of the os calcis. The clamp cannot get away from the foot because of the muslin ties.

greater force over all surfaces and allows the heel to be drawn down immediately, removing the necessity for continued traction.

Felt padding is then applied to the sole, extending around the heel and up to the knee. A snugly fitting plaster encasement is then adjusted from the toes to the upper part of the thigh; the knee is slightly flexed, with the foot in the position caused by slight talipes equinus, and a walking iron is incorporated. Elevation is insisted on for forty-eight hours, followed by walking on crutches, with weight bearing permitted after the tenth day. At the end of the second week the encasement is cut away above the knee. The plaster is removed at the end of the tenth week and physical therapy begun. Weight bearing is allowed at the end of the twelfth week, with a longitudinal arch support, made of firm felt or metal, in the shoe.

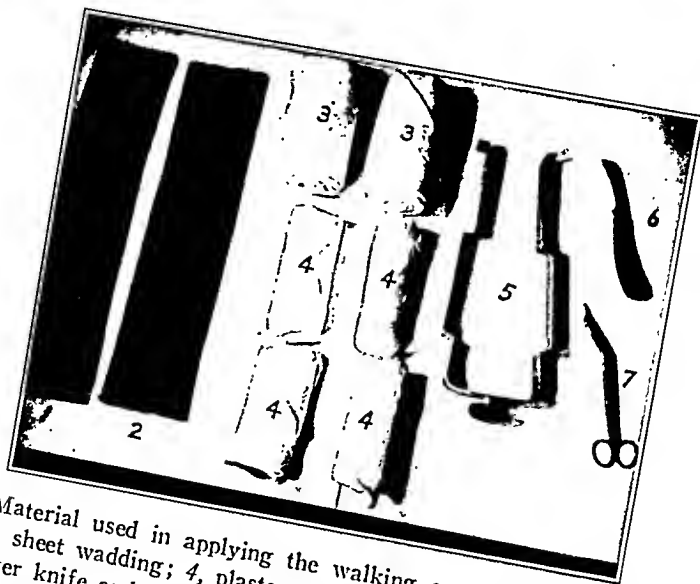


Fig. 7.—Material used in applying the walking cast: 1 and 2, long strips of black felt; 3, sheet wadding; 4, plaster of paris; 5, aluminum walking iron, and 6 and 7, plaster knife and scissors.



Fig. 8.—Application of the walking cast; manner of padding beneath the walking iron.



## REPORT OF CASES

CASE 1.—P. M., a man aged 52, fell 25 feet (7.6 meters), landing obliquely on one foot and crushing completely the right os calcis; the tuber joint angle was obliterated. Reduction was accomplished by molding the posterior portion of the foot with a special clamp, and immobilization was accomplished by applying a plaster of paris encasement, which was worn for ten weeks. Weight bearing was permitted after the fourteenth week, and the injured man returned to work after the twenty-fourth week.

CASE 2.—D. P., a man aged 42, jumped from a height of 16 feet (4.9 meters), landing on a hard concrete surface and suffering a compression fracture of the

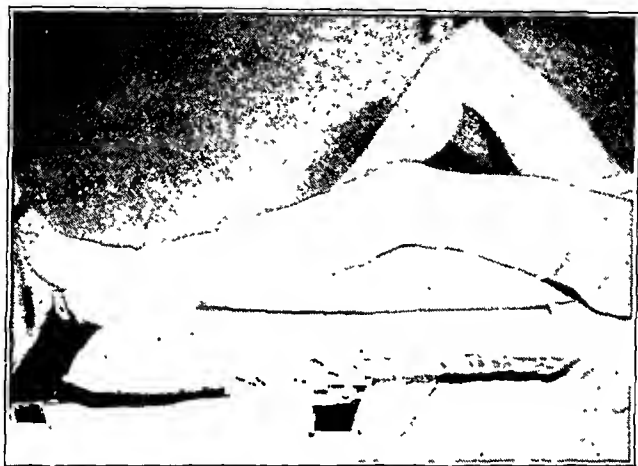


Fig. 9.—Walking cast completed and in position for drying.



Fig. 10.—Oxford worn, showing the type of leather and the longitudinal arch support of felt.

right os calcis. The tuber joint angle was obliterated, and the fragments were markedly displaced. Reduction of the fracture was accomplished by molding with special clamps while the patient was under general anesthesia. The tuber joint angle was restored, and a plaster of paris encasement incorporating a walking iron was applied. This was removed after the ninth week, and weight bearing was permitted after the eleventh week. The injured man returned to work after the thirteenth week. A spontaneous subastragalar arthrodesis materially aided his early recovery.

CASE 3.—H. B., a man aged 39, fell through the planking of a scaffold from a height of 12 feet (3.6 meters), fracturing his right os calcis. The fragments

were moderately displaced, so that a relatively small tuber joint angle resulted. Reduction was accomplished by molding with special clamps, and immobilization was accomplished by the application of a plaster of paris encasement. A walking block was incorporated in the plaster under the heel, a simple modification of a walking cast. This was removed after the eighth week, and weight bearing was permitted after the tenth week. The injured man returned to work after the seventeenth week, with all motion of the ankle and the foot completely restored.

CASE 4.—E. H., a man aged 25, fell through a scaffold onto a concrete surface 20 feet (6 meters) below. He suffered a comminuted fracture of the left os calcis, with moderate displacement, although the tuber joint angle remained practically normal. Reduction was easily accomplished by molding with special clamps, and a plaster encasement incorporating a walking iron was then applied. This encasement remained on for five weeks, and weight bearing was permitted after the sixth week. Pain was then confined about the subastragalar joint and proved intractable. A double arthrodesis was performed on the subastragalar joint, after which immobilization was maintained for eight more weeks. Two weeks after the removal of the plaster boot, weight bearing was permitted. The injured man returned to work after the twenty-fourth week.

CASE 5.—B. H., a man aged 42, fell from a height of 6 feet (1.8 meters) and landed on both heels on hard frozen ground. He suffered an oblique comminuted fracture of the right os calcis, with moderate displacement, although the tuber joint angle remained practically normal. Only lateral compression was necessary to reduce the fragment, and a plaster boot was applied and maintained for eight weeks. Weight bearing was permitted after the tenth week, and the injured man returned to work after the twelfth week.

CASE 6.—H. R., a man aged 40, fell from a girder 25 feet (7.6 meters) in the air, doing a complete somersault as he descended and landed on his heels and buttocks. He suffered a comminution of the right os calcis, with impaction in a distorted position, and a marked increase in the tuber joint angle. The impaction was broken up, and the fragments were molded into position by means of special clamps. A walking cast was maintained for eight weeks, and weight bearing was permitted after the twelfth week. The injured man returned to work after the twentieth week, with an excellent anatomic and functional result.

CASE 7.—J. W., a man aged 48, was accidentally pushed from the third floor of a building under construction and fell 60 feet (18 meters) onto a concrete base. He landed flat on his back, fracturing his skull, the spinous processes of the first and second lumbar vertebrae, the rami of the ischium and the pubis on the left side of his pelvis and crushing, or mushrooming, his left os calcis. When his condition would permit, his left os calcis was rebuilt, special clamps being used, so that the tuber joint angle was normal, and a plaster of paris encasement was applied. The encasement was maintained for six weeks, after which motion was begun. After the sixteenth week, when his general condition permitted, weight bearing was allowed and practically no pain occurred. He eventually made a complete recovery, but he was given a permanent disability rating of 50 per cent loss of the use of his left foot. Postreduction subastragalar arthritis seemed to be the cause of his pain. He refused further surgical intervention. This case was not used to compute the average length of disability, because of its complications.

CASE 8.—F. S., a man, aged 32, was precipitated down a brick shoot from 60 feet in the air, landing on a broken pile of bricks. He suffered a comminuted fracture of both his left and his right os calcis. The fractures were reduced by means of special clamps, and walking plasters were applied and maintained

for ten weeks. After the twelfth week weight bearing was permitted. After the sixteenth week the patient disappeared from the city, and he was not heard of for two years. When he returned he showed complete recovery of his left foot, but he had moderate postreduction traumatic arthritis of his right subastragalar joint. A double arthrodesis was done, and weight bearing was permitted after the sixteenth week. This patient is still under treatment, but a satisfactory result seems apparent.

In these cases the average age was 39 and the average fall 28 feet (8.5 meters). The patients were all men. Six of the fractures were on the right side and three on the left. The average period of disability was eighteen weeks. In five cases no percentage disability was allowed.

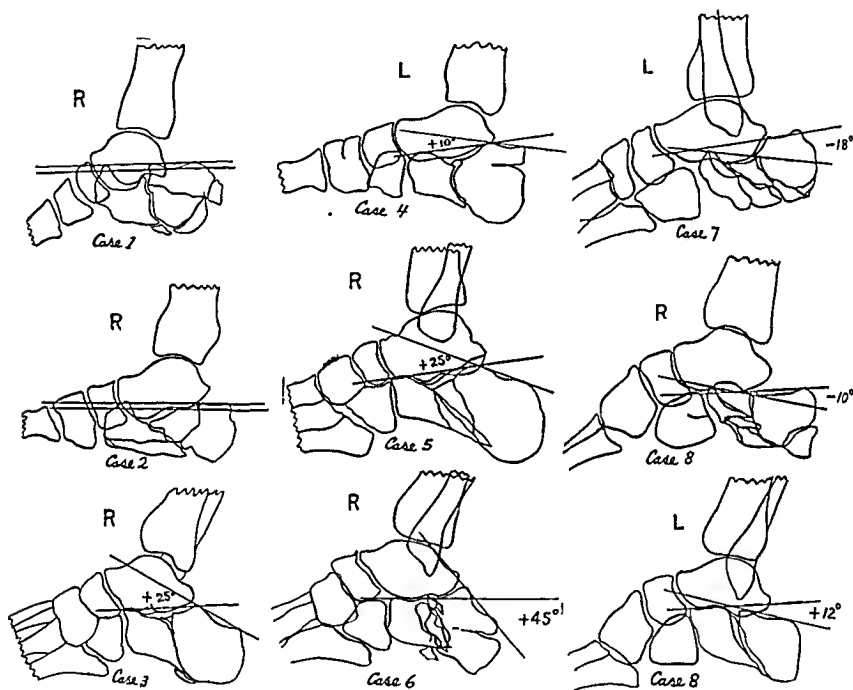


Fig. 11.—Tracings made from roentgenograms to illustrate the eight cases of fracture reported, with lines drawn to show the variety of tuber joint angles encountered.

In one case there was 10 per cent allowance and in another case 50 per cent. The treatment in one case is not completed.

#### RESULTS OF TREATMENT

Six of the 8 patients made a comparatively rapid recovery. One had post-traumatic arthritis in the subtaloid joint, refused arthrodesis and was given a 50 per cent disability allowance. The last patient disappeared for two years before treatment had been completed. When he returned his complaints were centered about the plantar surface of the

foot, and there was probably traumatic arthritis of the calcaneo-cuboid joint. The general architecture of the foot was excellent. This patient is still under treatment and was not considered when I determined the average length of disability.

While 8 cases are not many to report, there seems to be sufficient reason to offer this form of management of fracture for consideration. A crushed bone which is so accessible and which normally is so regular in shape should lend itself readily to molding if sufficient force can be applied without harm to the soft parts. The method is simple, effective, comfortable for the patient and physiologically reasonable and removes the necessity for tenotomy. Skeletal traction requires constant, skilled observation. The apparatus devised by Böhler requires rest in bed, is stationary and interferes with nursing care. This type of traction splint will some day be abandoned.

#### CONCLUSIONS

Fracture of the os calcis was formerly considered rare because it was not recognized. In 1835 Cooper detailed the best description and advocated "rest, elevation, until fragments consolidated." The use of this treatment persisted until the discovery of the roentgen ray, in 1895, after which manipulation and reduction were developed. The English propounded closed reduction, while the French turned to open operation with fixation and bone grafting. German and Austrian surgeons developed mechanics of the fracture and used skeletal traction for reduction, plus fixation. It was left for American surgeons to combine the many ways of approach and to work out the most generally acceptable methods. Cotton propounded a technic which holds today as the most universally used method.

Each surgeon has developed some slightly different attack, but all are together in their recognition of the difficulties in obtaining satisfactory results. Individual procedures are applicable to definite situations. The skill and judgment necessary for even passable results cannot be lightly considered. The more severe the fracture the more likely is a spontaneous arthrodesis to occur and the more excellent the result if the reduction is complete. Old, painful fractures call for a double or a triple arthrodesis. An occasional tenotomy may be necessary. Foreign body fixatives are used by some surgeons if comminution is not too great. Roentgen study must include at least four planes of visualization. An astragalectomy is never indicated. Skeletal traction in specialized apparatus gives good results if constant observation is possible. A restoration of the tuber joint angle, as described by Böhler, is essential. Closed reduction of a fresh fracture by forceful molding is recommended.

## SUMMARY

The methods reported in the literature are discussed.

A pictorial method, affording a rapid review of technic, is utilized.

According to the literature, there appears to be a tendency to discontinue the use of internal fixatives and to depend on closed reduction, forcible molding of fragments and skeletal traction. An old, painful fracture is best treated by double or triple arthrodesis.

More recent writers report shorter periods of disability.

Eight cases are reported in which closed forceful molding by means of a clamp and blocks was used.

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# COLLECTION OF AIR IN THE RIGHT SUB-DIAPHRAGMATIC SPACE

WITH SPECIAL REFERENCE TO HEPATODIAPHRAGMATIC  
INTERPOSITION OF THE COLON

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In the past decade, surgical literature has been replete with reports on eventration and on hernia of the diaphragm as well as on the role of the diaphragm in the surgical treatment of pulmonary tuberculosis, especially phrenicectomy and artificial pneumothorax. Articles in which the roentgenologic diagnosis of subphrenic abscess has been discussed are also available. There is, however, a dearth of material bearing on the significance of collections of air or gas under the diaphragm.

The presence of air in the subdiaphragmatic space is particularly pertinent when it is demonstrated roentgenologically to be on the right side, that is, between the diaphragm and the liver. In the left subphrenic area gas may be found in the cardiac end of the stomach (*Magenblase*) and in the splenic flexure of the colon, both of which lie directly beneath the leaf of the diaphragm. This is usually of no clinical importance. On the other hand, when gas or air occupies the space between the diaphragm and the liver, the finding signifies the presence of a pathologic condition or of some abnormality.

It is generally known that the right cusp of the diaphragm lies in direct contact with the superior surface, or dome, of the right lobe of the liver. During respiration in the normal state, the diaphragm and the liver move in unison. In a roentgenogram, their shadows merge and have the same density, so that one cannot be distinguished from the other. The histologic elements, such as the areolar tissue, the few blood vessels and the ligamentous attachment of the liver, that occupy the subphrenic space cast no differentiating shadows on the film. However, when this region is involved in a pathologic process, such as the presence of gas, fluid or tumefaction, which may cast a shadow of greater or less density than those of the liver and the diaphragm, or which by its presence may displace either one or both of these structures, a subdiaphragmatic lesion becomes evident in the roentgenogram. With the accumulation of air or gas in the subphrenic area, the potential space between the liver and the diaphragm becomes real. Gas is an excellent contrast medium, and by its presence the dia-

phragmatic dome and the superior surface of the liver are caused to stand out in silhouette.

#### CAUSES FOR THE PRESENCE OF SUBDIAPHRAGMATIC COLLECTIONS OF AIR

Air may be introduced into the subphrenic space either accidentally or for diagnostic purposes. In collapse therapy for tuberculosis or in the performance of an induced pneumothorax for diagnostic purposes, the needle may occasionally be introduced too low in the chest, so that the diaphragm is perforated and air is accidentally injected subdiaphragmatically before the operator is aware of the position of the needle (fig. 1). At times air is introduced under the diaphragm as a

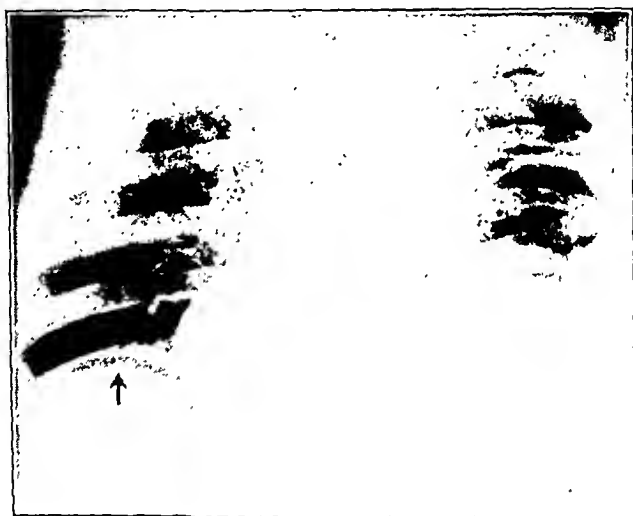


Fig. 1.—An accidental introduction of air under the right cusp of the diaphragm during thoracentesis (the patient in the erect position). The oblique view frequently shows the air to better advantage.

diagnostic procedure, in order to obtain a clearer visualization of the diaphragm or of the dome of the liver. In cases in which a neoplasm or cyst in this region is suspected, a diagnostic insufflation of air in the subphrenic space will reward the examiner with a clear portrayal of the existing pathologic conditions.

As a diagnostic procedure, air or gas is often introduced into the abdomen through the anterior abdominal wall (transabdominal pneumoperitoneum). With the patient in the erect or the semirecumbent position, the films show the accumulation of gas under the diaphragm. Similar findings obtain when air is introduced into the abdomen through the uterus and the patent fallopian tubes (tubal insufflation or Rubin test).

In the majority of cases, air can be demonstrated in the subdiaphragmatic space twenty-four hours or longer after an abdominal laparotomy (fig. 2). The accumulation of air may be very slight but is readily observed in the roentgenograms taken with the patient in the erect position.

#### ROENTGENOLOGIC APPEARANCE OF CONDITIONS OF AIR

When air between the diaphragm and the liver is free, it has a crescentic appearance, assuming the contour of the diaphragmatic dome above and the arch of the superior surface of the liver below. The air does not appear in the views which are taken with the patient in the prone position. However, when the patient assumes a semirecumbent or an erect posture, the air rises and collects under the diaphragm and so

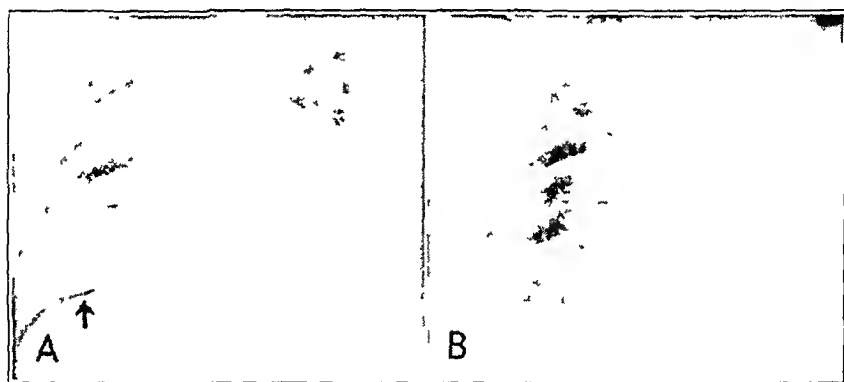


Fig 2—*A*, view of the chest of a patient in the erect position, taken three days after appendectomy. The presence of air between the diaphragm and the liver is clearly seen. *B*, view of the chest of the same patient in the horizontal position. The collection of air has disappeared, leaving a normal subdiaphragmatic space.

becomes visible in the film. The gas is sometimes better portrayed in oblique or lateral views.

Not infrequently, a subdiaphragmatic abscess may reveal a horizontal fluid level above which a pocket of gas is present, conforming with the dome of the diaphragm or taking the shape of the upper segment of a circle (fig. 3). This type of infection is caused by an anaerobic or gas-producing organism. The fluid level of the abscess is visualized roentgenologically in erect and lateral decubitus views and is obliterated in views taken with the patient in the prone position. The splash or succussion sound of the fluid and air in the abscess cavity can be elicited roentgenoscopically by shaking the patient. Similar roentgenologic observations prevail in cases of an abscess of the liver which contains gas and pus (fig. 4).

Apparent but not real evidence of the presence of air within the right subphrenic space is observed in patients with situs inversus. In these persons the gas-filled stomach lies in the right upper quadrant of

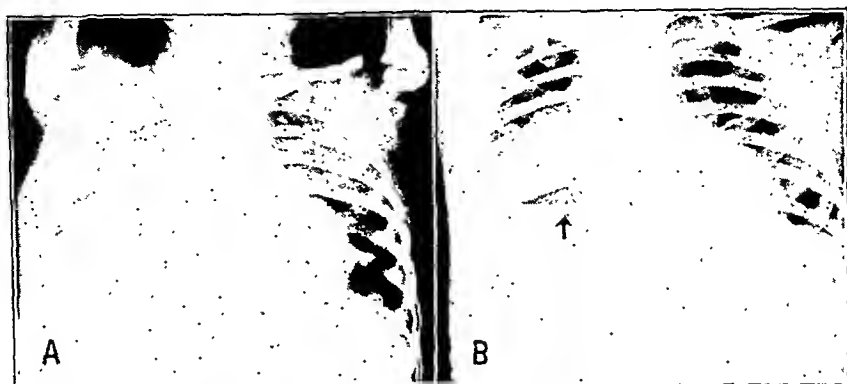


Fig. 3.—Abscess of the right subdiaphragm, showing the elevated cusp and the horizontal fluid level, above which the gas shadow is seen conforming to the dome of the diaphragm. *A*, roentgenogram of the chest of the patient in the prone position. *B*, view of the chest of the patient in the erect position.



Fig. 4.—Abscess of the liver in a 16 month old infant. *A*, the pocket of gas and the fluid level are visible in the posteroanterior view taken with the patient in the erect position. *B*, view of the chest of the same patient in the upright lateral position. *C*, view of the chest of the same patient in the lateral decubitus position, with the right side up.

the abdomen, immediately beneath the diaphragm, and simulates roentgenologically the appearance of air in the right subdiaphragmatic space. However, an error here is easily avoided by taking note of the right-

sided position of the heart and by observing the passage of an opaque meal through the transposed stomach.

From the clinical aspect, probably the most important cause for the presence of gas beneath the diaphragm is a perforated viscus. Gas escaping from a ruptured peptic ulcer collects in the subdiaphragmatic space when the patient assumes the upright position and is easily recognized on the films (fig. 5). The air disappears from the subphrenic area in the roentgenogram taken with the patient in the prone position. These well known observations have been considered indisputable. Wessler and Jaches<sup>1</sup> described these findings as "such a characteristic feature of the roentgen plate that it may be regarded as positive evidence of free air

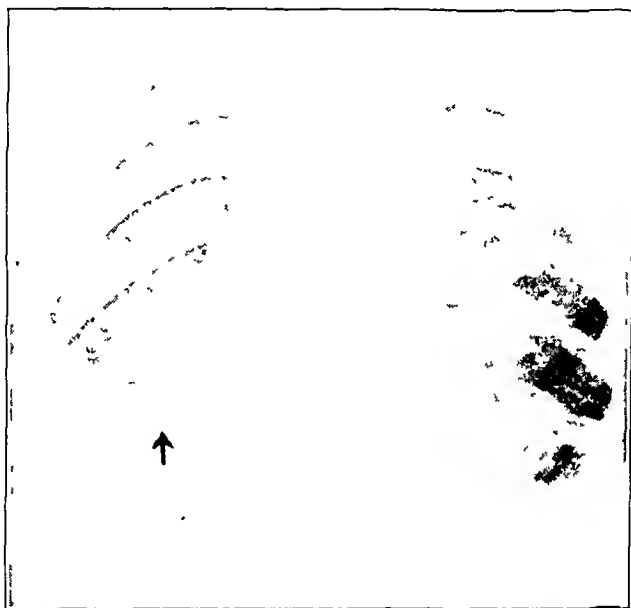


Fig. 5.—A collection of gas under the diaphragm in a patient with perforation of a duodenal ulcer.

or other gas in the peritoneal cavity." Nevertheless, there is another condition which may be readily confused with such a collection of gas and which must be borne in mind in order to avoid serious error.

In the normal person, the hepatic flexure of the colon is found immediately beneath the lower border of the liver. On rare occasions, however, this part of the colon may be found to lie between the diaphragm and the right lobe of the liver. Whether the malposition is congenital or acquired, it is usually observed on flat roentgenograms of the abdomen because of the presence of gas in the interposed segment

1. Wessler, H., and Jaches, L.: *Clinical Roentgenology of Diseases of the Chest*, Troy, N. Y., The Southworth Company, 1923, p. 509.

of the bowel. The gas-filled hepatic colon is visualized with the patient in the horizontal as well as in the vertical position. One must not confuse this anomalous position of the colon with eventration or herniation of the diaphragm. In hepatodiaphragmatic interposition of the hepatic flexure, the diaphragm is not displaced, and no part of the bowel lies in the chest cavity.

In the presence of this ectopic position of the gas-filled hepatic colon, how can the diagnosis of subdiaphragmatic air be made in a case of perforation of a hollow viscus? The condition of the left subphrenic region is often of little or no help, because of the frequent presence of gas in the stomach and splenic colon, which lie directly underneath the diaphragmatic leaf. The following case report illustrates the difficulty that may be encountered in arriving at the correct interpretation and emphasizes the importance of an exact interpretation of the gas shadow under the diaphragm.

#### REPORT OF CASES

CASE 1.—F. H., a Negress aged 45, a laundry worker, entered the Jewish Hospital with a history of severe abdominal cramps and vomiting for twenty-four hours. For the past year she had been troubled with "gas" and pyrosis following meals, and these conditions had become aggravated during the past week. Temporary relief was afforded by sodium bicarbonate. On the day prior to hospitalization the patient was suddenly seized with acute cramplike pains in the upper part of the abdomen and occasional vomiting. There was no bloody discoloration of the vomitus and stools. The symptoms persisted through the night and the following morning, at which time she was admitted to the hospital.

Physical examination showed a well developed, well nourished woman. The temperature was 100.4 F., the pulse rate 108 and the blood pressure 110 systolic and 74 diastolic. Except in the abdomen, the findings were normal. The abdomen was definitely rigid, and its lower half appeared distended. The rigidity was slightly more pronounced on the right side than on the left. Generalized rebound tenderness was present, most evident in the upper part of the abdomen and in the right lower quadrant. No masses were felt. Urinalysis gave negative results. The blood count showed 6,000 white blood cells with 66 per cent of polymorphonuclear leukocytes and a marked shift to the left. Plain roentgenograms of the abdomen taken in both the erect and the prone position revealed the manifestations of a pneumoperitoneum, as evidenced in both positions by the collection of a large amount of gas under the diaphragm. The diagnosis of a perforated viscus was ventured.

The patient was immediately operated on. The peritoneal cavity was opened by a right upper rectus incision. Cloudy fluid was obtained, and a pinpoint perforation on the anterior surface of the pylorus was found. Grayish grumous fluid was observed oozing through the opening. The perforation was closed. Peritonitis developed, and the patient died three days later.

*Comment.*—Although the findings at operation justified the roentgenologic conclusions, a review of the films on the following day raised several disturbing questions. Why was there still a large gas shadow in the subdiaphragmatic space in the views taken with the patient in the



prone position? What was the significance of the thin, dense bands traversing the collection of air? The opinion was expressed that the shadow between the diaphragm and the liver represented not free gas but an interposition of a gas-filled hepatic colon. The traversing thin bands were probably caused by the haustrations of the interposed bowel. The unchanged appearance of the gas shadow in views taken with the patient in both positions, erect and prone, indicated that there was a hepatodiaphragmatic interposition of the hepatic flexure. That free

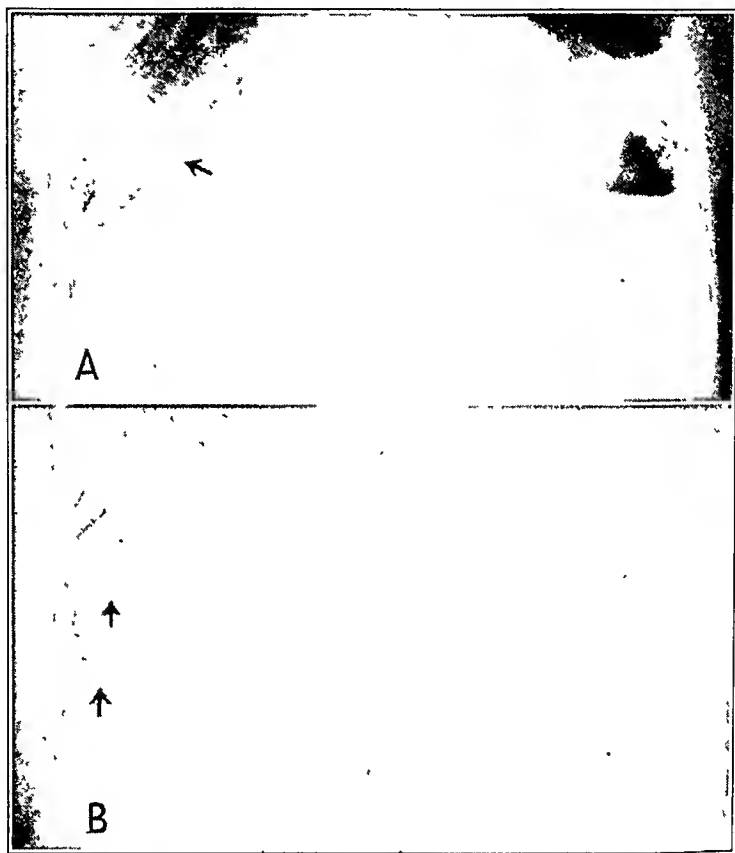


Fig. 6.—*A*, a large collection of subdiaphragmatic gas in a patient with a perforated prepyloric ulcer. Observe the fluid level on the right and the opaque band traversing the air collection (arrow). The roentgenogram was taken with the patient in the erect position. *B*, view of the chest of the same patient in the prone position. A considerable amount of gas is still present between the diaphragm and the liver. The fluid level has disappeared and several thin bands (arrows) are observed. The gas shadow represents a hepatodiaphragmatic interposition of the hepatic flexure, and the traversing bands indicate the haustral shadows. The films show the probable presence of free gas, as evidenced by the fluid level in the erect views in addition to the interposition of the gas-filled colon.

gas was present in the abdominal cavity and rose to the subphrenic space when the patient assumed the erect position was conjectural, since if so it would be obscured by the gas in the interposed bowel. However, the presence of a distinct fluid level in the views taken with the patient in the erect position indicated that, in addition to the meteoric hepatic flexure as revealed by its haustral bands, there were free air and fluid in the subphrenic space. In the roentgenograms taken with the patient in the prone position, with the air and fluid moving away from the diaphragm, the gas-filled bowel was observed unobscured between the liver and the diaphragm. Unfortunately the patient died on the third day after the operation; so further study was not possible. Permission for necropsy was not obtained.

Pendergrass and Kirk<sup>2</sup> reported a case of interposition of the hepatic flexure which was mistaken for free gas in the subdiaphragmatic area. The diagnosis of a ruptured viscus was made. At operation, acute pancreatitis was found. On reviewing the films the authors noticed for the first time the thin haustral bands traversing the gas pocket. Necropsy showed the liver to be rotated and low and the hepatic flexure interposed between the diaphragm and the liver. The case illustrates how an anomalous condition may closely simulate a serious surgical entity.

The following report of the case of a chronically ill patient illustrates a similar abnormal position of the hepatic flexure which had no bearing on the diagnosis.

CASE 2.—A. W., a white man aged 76, was admitted to the Brooklyn Cancer Institute with a history of difficulty in swallowing for four months. This symptom had become progressively worse until at the time of admission he was able to take liquids only. He had lost 45 pounds (20.4 Kg.) in the past four months. Until the onset of this illness, he had enjoyed good health, with no gastric or intestinal complaints.

On physical examination, he appeared well developed and showed evidence of recent loss of weight. The chest was normal except for a few basal rales. Percussion elicited normal diaphragmatic movement. He presented an indefinite mass in the right upper quadrant of the abdomen which did not move with respiration. The abdomen was soft, and normal hepatic dulness was obtained.

During a gastrointestinal roentgen examination a large collection of gas was observed between the diaphragm and the liver (fig. 7). The gas appeared continuous with the rest of the bowel and represented an interposition of the hepatic flexure, which could not be found in its usual position below the liver. Traversing the gas shadow were thin bands representing haustrations of the colon. Even when views were taken with the patient in the reclining position the gas shadow could not be obliterated. The remainder of the roentgenologic study showed the presence of a large filling defect deforming the cardiac end of the stomach and extending to the lower part of the esophagus, which showed a definite constriction, above which the lumen was considerably dilated. The

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2. Pendergrass, E. P., and Kirk, E.: Significance of Gas Under the Right Dome of the Diaphragm, *Am. J. Roentgenol.* **22**:238-246 (Sept.) 1929.

observations were highly suggestive of an advanced gastric malignant process extending to and encroaching on the esophagus.

In successive studies over a period of several weeks, the interposition of the hepatic flexure was not a constant observation. Although this interposition was present on most of the roentgenograms, on several of them the bowel was not shown to be interposed but remained abnormally high. These roentgen observations were clearly visualized with a barium sulfate meal. The right diaphragmatic cusp occupied a normal position and showed free respiratory excursions. Insufflation of the bowel with air (Bastedo), although not entirely satisfactory because of the patient's general weakness and his inability to cooperate, demonstrated an unusually high position of the hepatic flexure (fig. 8).

*Comment.*—In this case a chronically ill patient presented the clinical and roentgenologic evidence of a carcinoma of the cardia. An inci-



Fig. 7.—*A*, posteroanterior roentgenogram with the patient in the erect posture, showing a trace of gas in the right subphrenic space. Observe the faint shadow of a traversing haustral band (arrow). The view shows an interposition of the hepatic flexure between the liver and the diaphragm. *B*, view of the chest of the same patient in the oblique position. The gas-filled hepatic flexure and its haustral bands (arrows) are best seen in this view.

dental but inconstant observation was the high position of the gas-filled hepatic flexure, which frequently was demonstrated to be interposed between the diaphragm and the liver.

Both case reports present instances of hepatodiaphragmatic interposition of the hepatic flexure. In the first case the interposition tended to obscure the positive roentgenologic evidence necessary to establish the diagnosis of a ruptured viscus, and in the second the anomalous position of the hepatic flexure colon was apparently of no clinical importance. In both cases the roentgen findings were alike, namely, the presence of gas between the diaphragm and the liver, which sometimes

was observed to be continuous with the rest of the bowel, the clear outline of the haustral markings, the absence of the hepatic flexure in its usual position below the liver, and the persistence of the gas shadow in the views taken with the patient in the prone position.

#### PATHOGENESIS OF INTERPOSITION OF THE HEPATIC FLEXURE

According to Rogers,<sup>3</sup> the first case of hepatodiaphragmatic interposition was reported by Cantani in 1865. Bécclère<sup>4</sup> in 1899 described the roentgenologic findings. From that date, sporadic case reports appeared in the records until 1928, when Uspensky<sup>5</sup> recorded 8 cases.

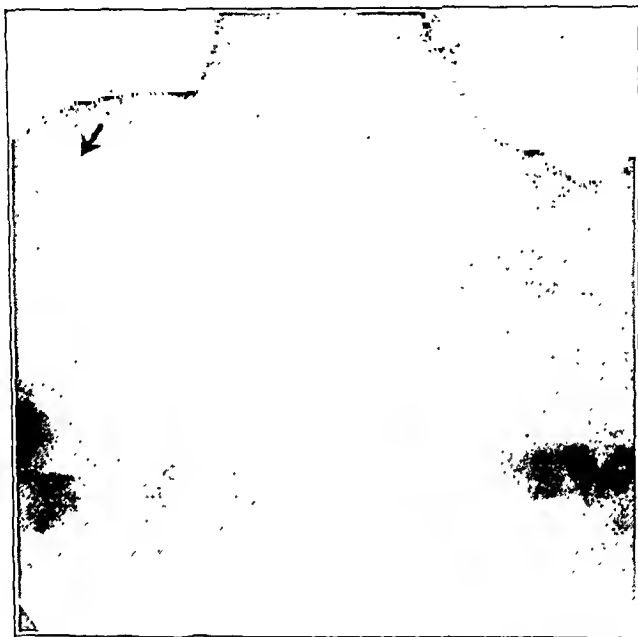


Fig. 8.—View of the chest of the patient six weeks later, after insufflation of the colon with air. The interposition was not permanent. However, the gas shows the unusually high position of the hepatic flexure (arrow).

of permanent and 14 of temporary interposition. Just<sup>6</sup> in 1929 reviewed the literature and presented 3 cases.

3. Rogers, J. C. T.: Hepato-Diaphragmatic Interposition of the Colon, Illinois M. J. **68**:264-268 (Sept.) 1935.

4. Bécclère, A.: Rectification d'une erreur de diagnostic: Ectopie du côlon transverse prise, a l'examen radioscopique, pour un abcès gazeux sousphrénique, Bull. et mém. Soc. méd. d. hôp. de Paris **16**:506-507 (May) 1899.

5. Uspensky, A.: Die pathogenetische Bedeutung des Symptomenkomplexes der "Interpositio colonis," Fortschr. a. d. Geb. d. Röntgenstrahlen **37**:540-555, 1928.

6. Just, E.: Zur Frage der Interpositio colonis, Deutsche Ztschr. f. Chir. **220**:334-354, 1929.

The exact causative factors in interposition are unknown. Usually, patients presenting its symptoms show an anomaly in the length of the transverse colon, which is the cause enabling the hepatic flexures to reach such a high position. Other factors are distention of the colon, with rotation on its mesentery, resulting in its elevated position in the abdomen (Viotor<sup>7</sup>), hepatoptosis, with or without shrinkage in the size of the liver and loss of its plasticity (Wessler and Jaches,<sup>1</sup> Assmann,<sup>8</sup> Dehn,<sup>9</sup> and Zucchi<sup>10</sup>), an anomalous development or weakness in the hepatic ligaments (Podkaminsky<sup>11</sup>) and varying degrees of weakness or malfunction of the diaphragm (Slavin<sup>12</sup>). Probably any one of these causative factors or a combination of several may operate in the production of interposition of the rising meteoric colon. When the close contact between the liver and the diaphragm is weakened by any of the causes just mentioned, whether it be paresis of the diaphragmatic cusp due to phrenicectomy on the right side, or ptosis and rotation of the liver as a result of its shrinkage or of defects in its ligamentous attachments, there is a predisposition to hepatodiaphragmatic interposition, provided the length of the colon is sufficient to enable it to rise to this unusual position.

Uspensky,<sup>5</sup> however, stated that as a result of inflammation in the region of the colon adhesions form which fix the bowel in a bizarre position. Soupault,<sup>13</sup> Trémolières and Pierron,<sup>14</sup> Trémolières and Tardieu,<sup>15</sup> Bürger<sup>16</sup> and Weiland<sup>17</sup> emphasized the possibility that some

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7. Viotor, A. C.: Anatomic Basis for the Study of Splanchnoptosis, *Arch. Surg.* **28**:659-683 (April) 1934.

8. Assmann, H.: *Die klinische Röntgendiagnostik der inneren Erkrankungen*, ed. 4, Leipzig, F. C. W. Vogel, 1929, p. 788.

9. Dehn, O.: Ein Fall von Lungentumor mit ungewöhnlichem Röntgenbefund, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **34**:333-334, 1926.

10. Zucchi, L.: L'interposizione epatodiaframmatica del colon, *Riforma med.* **49**:882-888, 1933.

11. Podkaminsky, N. A.: Zur Frage nach den Ursachen der Interposition von Organen zwischen Diaphragma und Leber, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **36**:327-333, 1927.

12. Slavin, P.: Interposition of the Colon Following Induced Phrenic Paralysis, *Am. J. Roentgenol.* **33**:481-485 (April) 1935.

13. Soupault, R.: Interposition inter-hépatodiaphragmatique du côlon. Diverticule du duodénum. Ulcus térébrant du duodénum, *Arch. d. mal. de l'app. digestif* **20**:350-355 (March) 1930.

14. Trémolières, F., and Pierron, E. J. M.: L'interposition hépatodiaphragmatique du côlon, *Presse méd.* **38**:1-3 (Jan. 1) 1930.

15. Trémolières, F., and Tardieu, A.: L'interposition hépatodiaphragmatique du côlon, *Arch. d. mal. de l'app. digestif* **21**:1154-1197 (Dec.) 1931.

16. Bürger, M.: Zur Klinik der Leberdystopien, *Klin. Wchnschr.* **4**:102-107, 1925.

17. Weiland, W.: Ein röntgenologisches Phänomen bei perforiertem Magengeschwür, *Munchen. med. Wchnschr.* **62**:537-538 (April) 1915.

type of inflammatory process, such as a perforating duodenal or pyloric ulcer, may result in the formation of pericolic adhesions which fix the hepatic flexure in an abnormal site. According to Podkaminsky,<sup>11</sup> abnormal intra-abdominal pressure tends to weaken the contact between the liver and the diaphragm and to produce interposition.

#### SYMPTOMS AND TREATMENT

Often there are no clinical symptoms, and the condition may be found accidentally during a roentgenographic examination for other reasons (case 2). However, not infrequently these patients are of the visceroptotic type and complain of localized or generalized abdominal pain, which may radiate to the right shoulder or be referred to the abdomen and which is aggravated by deep inspiration. Abdominal distention and constipation are often present. Anterior hepatic dulness may be lost, and a mass formed by the displaced liver may be palpable in the right lower quadrant of the abdomen. The clinical picture is frequently overshadowed by some other organic lesion, such as cholecystitis, peptic ulcer or intestinal obstruction. Roentgenologic examination establishes the diagnosis.

If the symptoms are mild, conservative measures are employed to relieve the discomfort caused by meteorism and constipation. However, when a permanent incarceration of the bowel produces severe symptoms, surgical intervention is suggested, and some form of hepatopepy is performed.

#### SUMMARY

The causes for accumulation of gas in the right subdiaphragmatic space are enumerated, and their recognition in the roentgenograms is described. Two cases of hepatodiaphragmatic interposition of the hepatic flexure are reported. In the first case this lesion was confused with gas in the subphrenic space from a ruptured peptic ulcer; in the second it appeared as an accidental finding. Finally, a brief résumé is given of the history and pathogenesis of the causative factors in the production of interposition, and mention is made of the possible symptoms and management of this anomalous condition.

# MECHANICS OF SIMPLE INTESTINAL OBSTRUCTION

## AN EXPERIMENTAL STUDY

LOUIS SPERLING, M.D.

MINNEAPOLIS

An enormous amount of research has yielded considerable information about intestinal obstruction and has resulted in the modification of previous concepts. Admitting that progress has been made, it is evident from a perusal of recent figures on mortality that much remains to be learned. Christopher,<sup>1</sup> Miller<sup>2</sup> and others have recently reported mortality rates varying between 40 and 60 per cent. When a disease carries such a mortality, no apology need be made for presenting further experimental studies. The fact that over 5,000 articles dealing with intestinal obstruction are on file in the library of the Surgeon General is an indication of the interest of physicians in this disease and an admission that their knowledge of the subject is far from complete.

It is evident that when complete knowledge of the physiologic changes that occur in intestinal obstruction is acquired, physicians will be better equipped to cope with the problem. Any alteration of normal physiology which takes place must be secondary to the stasis which is the immediate effect of intestinal obstruction. Stasis leads to distention and to an increase of intraenteric pressure, and these are the primary causes of the complications which appear when obstruction occurs. The effect of distention on the wall of the bowel is best stated in terms of the effect of various degrees of increased intraluminary pressure. This work deals with the subject of increased intraenteric pressure as it occurs in simple ileal obstruction and the effects of such pressure on the structure, the function and the permeability of the intestinal wall.

This presentation is concerned only with a study of the mechanism of simple obstruction of the ileum. The problem of strangulation obstruction is not of concern here, except as features of strangulation may attend increased intraenteric pressure. A consideration of the

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Abridgment of thesis submitted to the Faculty of the Graduate School, University of Minnesota, in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Surgery.

1. Christopher, F., and Jennings, W. K.: Mortality in Intestinal Obstruction, *Ann. Surg.* **99**:332-337, 1934.

2. Miller, C. J.: A Study of Three Hundred and Forty-Three Surgical Cases of Intestinal Obstruction, *Ann. Surg.* **89**:91-107, 1929.

various clinical types of obstruction also lies outside the province of this paper. The work is confined to a study of ileal obstruction for two reasons: First, there is a comparative dearth of experimental observation on this type of obstruction as compared with an abundance of material on high intestinal obstruction. Second, the cause of death following low ileal obstruction is still obscure, while the lethal factors in simple high intestinal obstruction are fairly well understood. Whenever possible, an effort has been made to compare the effects of various experimental conditions on the normal intestinal wall with their effects on the wall of the obstructed intestine.

#### INTRAENTERIC PRESSURE IN INTESTINAL OBSTRUCTION

In order to determine the effect of increased intraenteric pressure on the intestinal wall it is necessary first to know what degree of pressure is present in experimental and in clinical cases of intestinal obstruction.

The normal sustained intrainestinal pressure in dogs is 2 to 4 cm. of water (Owings and others<sup>3</sup>). In simple obstruction of the ileum the sustained pressure may be increased to 8 cm. of water. In closed jejunal loops Burget<sup>4</sup> has recorded pressures as high as 50 or 60 cm. of water. It is evident that the pressure reached a higher level in a shorter period in closed ileal loops than in simple obstruction, in which the bowel may empty itself by reversed peristalsis and regurgitation.

Stone and Firor<sup>5</sup> recorded a pressure of 150 cm. of water in a patient with low ileal obstruction of several hours' duration. As far as can be determined, this is the only clinical measurement, besides my own, of the pressure in intestinal obstruction in man. Elman and Aird<sup>6</sup> measured the intraenteric pressure in a human being with a jejunal fistula. A sustained pressure varying from 2 to 4 cm. of water was noted. During peristalsis the pressure rose rapidly, reaching 15 to 27.5 cm. of water. Minor peristaltic waves up to 6 or 7 cm. of water were frequent. With increased peristalsis there was always associated mild hypogastric discomfort. Colic was present when the pressure

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3. Owings, J. C.; McIntosh, C. A.; Stone, H. B., and Weinberg, J. A.: Intra-Intestinal Pressure in Obstruction, *Arch. Surg.* **17**:507-520 (Sept.) 1928.

4. Burget, G. E.; Martzloff, K.; Suckow, G., and Thornton, R. C. B.: Closed Intestinal Loop: I. Relation of the Intraloop (Jejunum) Pressure to the Clinical Condition of Animal, *Arch. Surg.* **21**:829-837 (Nov.) 1930.

5. Stone, H. B., and Firor, W. M.: Absorption in Intestinal Obstruction: Intra-Intestinal Pressure as a Factor, *Tr. South. S. A.* **37**:173-184, 1924.

6. Elman, R., and Aird, I.: Observations on Intra-Intestinal Pressure with Reference to Absorption of Saline, *Proc. Soc. Exper. Biol. & Med.* **32**:1620-1622, 1935.



reached 20 cm. of water. On one occasion, after the intake of food, a pressure of 35 cm. of water was noted.

The intraenteric pressure was determined in 25 dogs with low ileal obstruction of one to seven days' duration.<sup>7</sup> The pressure ranged from 4 to 19 cm. of water, or roughly four times the normal pressure. Active peristalsis was uniformly present even after seven days of obstruction (fig. 1). The intraenteric pressure in this series apparently increased with the duration of the obstruction. It was observed that the sustained pressure in low ileal obstruction was seldom above 14 cm. of water (table 1). These data are in accord with the findings of Owings and his associates.<sup>3</sup>

Opportunity has also been afforded to determine the intraenteric pressures at the time of the operation in 6 clinical cases of mechanical

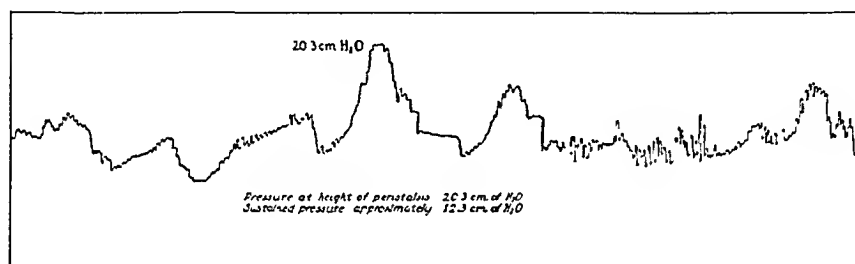


Fig. 1.—Intraenteric pressure and peristalsis in simple ileal obstruction of seven days' duration. (Pressure at height of peristalsis, 20.3 cm. of water; sustained pressure, approximately 12.3 cm. of water.)

TABLE 1.—Sustained Intraenteric Pressure in Dogs with Simple Ileal Obstruction

Dog	Duration of Obstruction, Days	Pressure, Cm. H <sub>2</sub> O	Dog	Duration of Obstruction, Days	Pressure, Cm. H <sub>2</sub> O
1	1	8	11	4	14
2	2	4	12	4	10
3	2	6	13	4	7
4	2	12	14	4	12
5	2	6	15	4	10
6	3	10	16	4	8
7	3	12	17	4	10
8	4	8	18	7	19
9	4	10	19	7	12
10	4	14			

obstruction of the small bowel.<sup>8</sup> The sustained pressure varied between 4 and 18 cm. of water. With peristaltic activity, pressures rose to 20 and then to 30 cm. of water.

7. Sperling, L.; Paine, J. R., and Wangenstein, O. H.: Intra-Enteric Pressure in Experimental and Clinical Intestinal Obstruction, *Proc. Soc. Exper. Biol. & Med.* **32**:1504-1506, 1935.

8. Sperling, L.: Role of the Ileo-Cecal Sphincter in Cases of Obstruction of the Large Bowel, *Arch. Surg.* **32**:22-49 (Jan.) 1936.

Pressures were observed at operation when colostomy was performed for the relief of distention in 8 cases of acute obstruction of the colon. The sustained pressure varied between 12 and 52 cm. of water; in 6 cases pressures above 23 cm. of water were recorded, much higher pressures than were observed in cases of obstruction of the small bowel. The significantly greater pressure in obstruction of the colon is due to the action of the ileocecal sphincter, which makes the colon virtually a closed loop, in which the intraenteric pressure usually greatly exceeds pressures observed in simple ileus. These observations have been reported at greater length elsewhere.<sup>8</sup>

#### INFLUENCE OF SIMPLE OBSTRUCTION ON THE PHYSICAL CHARACTER OF THE INTESTINAL WALL

There is relatively little in the literature concerning the changes in the physical character of the wall of the bowel following simple obstruction. In the following sections, a detailed study is presented of the influence of simple mechanical ileus on the length, the weight, the water content, the blood content, and the strength of the intestinal wall.

#### INFLUENCE OF OBSTRUCTION ON THE LENGTH OF THE BOWEL

According to several investigators the first response of the bowel of the guinea pig to distention is a contraction of the longitudinal muscles (Trendelenburg,<sup>9</sup> Crane and Henderson<sup>10</sup>). This produces a decrease in length which amounts to as much as 20 or 25 per cent of the entire length of the bowel. Van der Reis and Schembra<sup>11</sup> presented observations to show that the functional length of the small bowel is only 2.2 to 2.7 meters, or 6 to 15 feet. They contended that in the living person the bowel is much shorter than in the cadaver, in which it usually measures about 22 feet (6.6 meters). In instances of fistula in the terminal ileum, a catheter 6 to 9 feet (1.8 to 2.7 meters) long was found to suffice for the entire length of the small bowel.

No definite information is available as to the effect of obstruction on the length of the bowel. Because of the difference of opinion among clinicians concerning this matter, it was felt worth while to investigate it. It was found that in experimental simple obstruction of the ileum

9. Trendelenburg, P.: Physiologische und pharmakologische Versuche über die Peristaltik des Dünndarms, *Arch. f. exper. Path. u. Pharmakol.* **81**:55-129, 1916-1917.

10. Crane, J. W., and Henderson, V. E.: The Sensitivity of the Small Intestine at Different Levels to Internal Pressure, *Am. J. Physiol.* **70**:22-25, 1924.

11. van der Reis and Schembra, F. W.: Weitere Studien über die funktionelle Darmlänge; operative Ergebnisse und Beobachtungen an Bauchfenster, *Ztschr. f. d. ges. exper. Med.* **52**:74-83, 1926.

there was a definite shortening of the intestine (Sperling and Wangenstein<sup>12</sup>). The length of a segment which before obstruction measured 12 inches (30 cm.) decreased by as much as one third after obstruction. Statistically, it was shown that the intestine is shortened to a significant degree in simple ileal obstruction. Hypertonicity of the obstructed intestine, with marked contraction of the longitudinal muscles, is probably responsible for this shortening. The shortening is sufficient to account for some of the increased weight of the wall of the bowel which is observed in simple ileal obstruction.

TABLE 2.—*Shortening of the Bowel in Simple Ileal Obstruction—Ultimate Length of Consecutive 12 Inch Segments from Site of Obstruction, Ileum to Jejunum*

Dog	Duration of Obstruction, Days	Segments								
		1	2	3	4	5	6	7	8	9
1	4	8.75	9.00	7.50	9.00	....	....	....	....	9.50
2	4	12.00	12.00	8.50	9.50	9.50	....	....	....	9.50
3	4	9.50	9.00	8.00	7.00	....	....	....	....	....
4	4	8.25	7.00	7.25	7.25	....	....	....	....	7.75
5	4	7.25	6.75	7.00	7.00	8.25	8.50	....	....	8.25
6	4	9.25	8.75	8.50	13.50	6.75	....	....	....	7.25
7	2	9.50	10.00	10.00	11.50	10.50	12.00	11.00	....	9.00
8	2	8.75	8.25	7.75	8.75	7.75	8.50	9.25	11.00	10.00
9	1	10.50	10.50	(Only two lower segments marked off)						
10	1	8.50	5.50	(Only two lower segments marked off)						
11	3	10.00	8.00	(Only two lower segments marked off)						
12	3	8.50	9.75	(Only two lower segments marked off)						
Average shortening: $-2.77 \pm 0.35$ inches; $-3.47 \pm 0.40$ inches										

TABLE 3.—*Length of Consecutive 12 Inch Segments of the Small Intestine of Normal Dogs Measured After Forty-Eight Hours (Ileum to Jejunum)*

Dog 1.....	12.00	11.25	12.5	13.00	9.5	12.00	12.50	13.5	13.00	11.00		
Dog 2.....	11.25	13.25	11.0	11.25	11.0	10.25	10.25	12.0	10.75	10.25	10.25	11.0
Average decrease in length of $0.63 \pm 0.23$ inch												

#### INFLUENCE OF OBSTRUCTION ON THE WEIGHT OF THE INTESTINAL WALL AND ON ITS CONTENT OF WATER AND HEMOGLOBIN

As far as can be determined, there has been no previous estimation of changes in the weight of the intestine in simple intestinal obstruction. Opportunity to make such observations was afforded in the course of other experiments on dogs with simple obstruction of the ileum.

12. Sperling, L., and Wangenstein, O. H.: Influence of Obstruction of the Bowel upon Its Length and Weight, *Proc. Soc. Exper. Biol. & Med.* **32**:1219-1224, 1935.

The weight of the ileum immediately above the site of obstruction was determined to be 114 per cent greater than that of the normal ileum (Sperling and Wangenstein<sup>12</sup>). When the factor of shortening of the bowel was eliminated, the true gain in weight was found to be 34 per cent (table 6). Comparisons of the water content of the normal and that of the obstructed bowel showed an average increase of about 7 per cent in the ileum above the site of obstruction and an average

TABLE 4.—*Weight of Consecutive Feet of Normal Intestine from the Ligament of Treitz to the Terminal Portion of Ileum*

Dog	Weight, Kg.	Weight of Consecutive 1 Foot Segments of Bowel, Jejunum to Ileum, Gm.
1	16	47-40-40-45-43-43-39
2	21	36-38-40-40-37-29-26
3	40	46-44-42-42-47-44-40-36
4	22	39-35-32-32-30-25-20-24-20-25-24
5	25	42-40-40-39-36-38-35-35-34
6	8	37-33-30-32-26-18
7	14	34-33-32-32-30-26-22-20-23-21
8	17	45-39-37-33-29-30-29
9	18	40-34-27-32-33-30-29
10	22	
Average weight.....	20	Av. wt. of 1 foot of terminal ileum, 28.7 Gm.

TABLE 5.—*Weight of Consecutive Feet of Obstructed Intestine from the Ligament of Treitz to the Site of Obstruction in the Terminal Portion of the Ileum*

Dog	Weight, Kg.	Duration of Obstruction, Days	Weight of Consecutive 1 Foot Segments of Bowel, Jejunum to Ileum, Gm.
1	18	7	42-45-51-52-62-70-60-85
2	19	8	41-34-36-36-42-40-41-49-68
3	19	6	52-45-40-54-50-43-62
4	19	5	46-44-36-50-55
5	23	6	39-43-48-42-48-62
6	17	6	43-52-50-39-46-55
7	16	7	42-46-46-54
8	18	5	39-39-43-56
9	12	7	30-34-49-52-48
10	15	5	56-56-58-72
11	19	7	29-21-20-10-23-26-30-51
Average weight.....	17		Av. wt. of terminal ileum per ft., 60.7 Gm. Percentage of increase, 114

increase of 4.7 per cent in the jejunum remote from the obstruction (table 7). There is evidently no dehydration of the wall of the bowel even though the systemic tissues are desiccated and the blood is concentrated.

The weight per foot of the normal small intestine usually decreases from the duodenum to the terminal portion of the ileum. There seems to be a downward gradient even in weight. In simple ileal obstruction there is a reversal of the normal gradient in weight; that is, weight of the ileum is greatest above the site of obstruction and there is a

decrease in weight in a retrograde manner from the obstructed ileum to the duodenum. This is due to the fact that the segments of bowel immediately above the obstruction increase most in weight while those segments of the jejunum remote from the site of obstruction increase only slightly in weight.

The results indicated in table 8 represent the relative increase in hemoglobin content of the obstructed bowel as compared with that of the

TABLE 6—*Weight Changes of the Bowel in Simple Ileal Obstruction (1 Foot Segments Marked Off at the Time Obstruction Was Made)*

Dog	Weight, kg	Duration of Obstruction, Days	Weight of Consecutive 1 Foot Segments of Bowel, Jejunum to Ileum, Gm	
1	14	4	40—32—31—26—29—32—41	
2	13	4	21—22—23—30—34	
3	14	4	41—45—44—42—37—58	
4	18	4	27—25—35—33—37—35	
5	8	4	23—16—18—19—35	
6	17	4	31—31—35—50	
7	10	4	24—20—21—21—27—27—39	
8	11	2	22—22—20—19—23—22—26	
9	13	2	25—24—23—23—23—24—26—30	
10	14	3	21—20—22—22—29—37	
Average weight	13		Average weight of terminal portion of ileum per foot . . . . . 38.5 Gm	
			Percentage of increase . . . . . 34	

TABLE 7—*Water Content of Normal Bowel as Compared with Obstructed Bowel*

Normal Bowel			Obstructed Bowel		
Dog	Jejunum %	Ileum, %	Dog	Jejunum, %	Ileum, %
1	76.5	72.6	1	82.4	85.1
2	79.6	78.1	2	84.7	85.0
3	76.3	78.2	3	84.1	80.5
4	77.2	77.2	4	78.0	80.9
5	78.1	77.7	5	77.4	83.3
6	76.2	75.5	6	83.3	85.4
7	75.9	77.8	7	81.2	81.2
8	70.2	72.7	8	81.0	78.4
9	77.4	77.5	9	80.4	83.5
Average	76.3	76.5	Average	81.0	83.5
Mean difference	$\pm 1.7$	$\pm 1.73$	Mean difference	$\pm 2.39$	$\pm 2.02$

In simple ileal obstruction there is approximately 4.7 per cent increase of the water content of the jejunum and 7 per cent increase of the water content of the ileum.

normal bowel (experiment performed on the same dog prior to obstruction). There is a wide range of individual variation. It is noteworthy that an increase of more than 100 per cent is the rule. A previous study made in this laboratory by Carlson and Wangenstein<sup>13</sup> indicated that the accumulation of blood in the bowel in simple obstruction is due to stasis in the vessels and not to interstitial hemorrhage.

13 Carlson, H. A., and Wangenstein, O. H.: Histologic Study of the Intestine in Simple Obstruction, *Proc. Soc. Exper. Biol. & Med.* 29:421-424, 1932.

These observations may be briefly summarized as follows:

1. The wall of the bowel above the site of a simple ileal obstruction increases more than 100 per cent in weight.
2. When the factor of shortening of the bowel is eliminated, there is an actual increase in weight of 34 per cent.
3. Edema of the intestinal wall accounts for only 7 per cent of the increase in weight.
4. The increase of blood in the wall of the bowel is the most important factor in the actual increase in its weight.

#### INFLUENCE OF OBSTRUCTION OF THE BOWEL ON ITS TENSILE STRENGTH (BURSTING STRENGTH)

The changes in the bowel in intestinal obstruction due to increased intraenteric pressure have been emphasized by many investigators.

TABLE 8.—*Comparative Increase of Hemoglobin in the Blood of the Bowel Wall in Simple Obstruction*

Dog	Duration of Obstruction, Days	Comparative Increase, Times Normal
1.....	1	5.34
2.....	1	2.76
3.....	2	3.22
4.....	2	2.80
5.....	3	1.40
6.....	3	1.26
7.....	4	10.65
8.....	4	7.17
9.....	4	2.75
10.....	4	4.54

Perforations of the bowel due to gangrene are sometimes terminal complications of simple intestinal obstruction.

A study was made to compare the bursting pressure of the wall of the normal bowel with that of the bowel in simple intestinal obstruction (Sperling and Wangenstein<sup>14</sup>). The normal ileum of the dog in most cases was found able to withstand greater degrees of pressure than could the jejunum. The ileum resisted pressures varying between 300 and 1,000 mm. of mercury. The bursting pressure of the jejunum fell within the same limits, but in almost every case was lower than that of the ileum in the same dog. This fact, however, could not be proved to be statistically significant.

In the dogs with intestinal obstruction the reverse was found to be true. The jejunum, that is, that portion of the bowel farthest away from and least affected by the obstruction, was the more resistant.

14. Sperling, L., and Wangenstein, O. H.: Influence of Obstruction of the Bowel on Its Strength (Bursting Strength), *Proc. Soc. Exper. Biol. & Med.* 32:1183-1185, 1935.

The tensile strength of the jejunum approached the normal, whereas that of the obstructed segment of bowel (ileum) was far below normal. In the obstructed specimens (ileum) the serosa usually split at the antimesenteric border at a pressure of about 100 to 300 mm. of mercury and soon burst, whereas in the specimens of normal ileum the serosa was usually able to resist a pressure of more than 400 mm. of mercury.

TABLE 9.—*Tensile Strength (Bursting Pressure) of Normal Bowel* \*

Dog	Pressure (Mm. Hg) at Which Serosa Split		Pressure (Mm. Hg) at Which Bowel Burst	
	Ileum	Jejunum	Ileum	Jejunum
1.....	360 a	210 a	620	400
2.....	300 a	660 a	560	660
3.....	540	400 p	540	400
4.....	480 a	440	480	440
5.....	660 a	600 a	Ends blew out	
6.....	540 a	610 a	Ends blew out	
7.....	790 a	540 a	700	540
8.....	1,060 a	820 a	1,060	820
9.....	560 p	640 p	560	640
10.....	700 p	750 a	700	780
11.....	300 m	220 m	660 m	500 a
12.....	1,080 m	400 a	1,080	820
Mean.....	606.7	526.7	696	600

\* In this table a indicates antimesenteric border; p, paramesenteric border, and m, mesenteric border.

TABLE 10.—*Tensile Strength (Bursting Pressure) of Obstructed Bowel* \*

Dog	Duration of Obstruction, Days	Pressure (Mm. Hg) at Which Serosa Split		Pressure (Mm. Hg) at Which Bowel Burst	
		Ileum	Jejunum	Ileum	Jejunum
1.....	6	195 a	...	200-End b. o.	
2.....	6	220 a	240	230	540
3.....	7	200	260	250	225
4.....	7	90 a	190 a	180 a	260 a
5.....	7	200	200	200	200
6.....	7	200 a	500 a	280	760
7.....	5	210 a	420 a	250 m	620 m
8.....	5	360 a	560 p	480 m	560 p
9.....	5	260 a	360 a	360 a	400 a
10.....	6	400 m	500	460 m	520 a
Mean.....		233.51	352.2	292.0	453.9

\* In this table a indicates antimesenteric border; p, paramesenteric border, and m, mesenteric border.

These observations appear to justify the following conclusions:

1. The intestinal wall in simple obstruction cannot withstand as high an intraenteric pressure as can the wall of the normal bowel.

2. The portion of the bowel just above the site of obstruction is most affected.

3. The most frequent site of tearing of the serosa and of rupture is the antimesenteric border of the bowel.

## INFLUENCE OF SIMPLE INTESTINAL OBSTRUCTION AND OF INCREASED INTRAENTERIC PRESSURE ON THE FUNCTION OF THE BOWEL

Much evidence has accumulated to show that distention, with its increased intraenteric pressure has a pernicious effect on the function of the bowel. Distention produces an alteration in normal physiology which is sufficient to explain many of the findings in cases of intestinal obstruction.

### EFFECT OF DISTENTION ON INTESTINAL TONE AND PERISTALSIS

It is recognized that a certain degree of intraenteric pressure acts as a stimulus to peristaltic activity. Ganter<sup>15</sup> and others have determined that a certain critical pressure must be reached in the bowel before peristalsis begins. Below this pressure, which is estimated to be 15 cm. of water (Ganter) for man, peristalsis ceases. This pressure varies from person to person but remains constant in the same person at all times. The normal frequency of peristalsis in the duodenum of man is from 10 to 12 waves per minute. If the pressure is maintained above the critical level, regular rhythmic contractions set in. There is no increase in rate but there is a definite increase in the height of the individual contractions.

Unstriated muscle responds to an increased load (stretch stimulus) with a more powerful contraction. The load in intestinal obstruction is the distention incident to stasis. If peristalsis is absent, it is induced by distention. Bayliss and Starling<sup>16</sup> in 1899 showed that distention resulted first in slight augmentation of the contractions of the intestine, and that prolonged distention produced a strong tonic contraction with rhythmic intermissions. In 1923 Bauer<sup>17</sup> showed that sustained elevated intraenteric pressure resulted at first in increased peristalsis, which disappeared with fatigue. After a short period, peristalsis reappeared, to complete a cycle of alternate activity and rest. I have made the same observation in loops of the intestines of dogs subjected to pressures varying between 20 and 100 cm. of water for a period of one hour. This phenomenon corresponds well to the intermittent cramplike pains suffered by patients with mechanical intestinal obstruction.

*Critical Pressure.*—The pressure within closed ileal loops was gradually increased by filling the lumen with water at a temperature of 35 to 40 C. Peristalsis

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15. Ganter, G.: Experimentelle Untersuchungen über die Peristaltik des menschlichen Dünndarmes, Arch. f. d. ges. Physiol. **201**:101-116, 1923.

16. Bayliss, W. M., and Starling, E. H.: The Movement and Innervation of the Small Intestine, J. Physiol. **24**:99-143, 1899.

17. Bauer, M.: Studien über die Dünndarm Peristaltik, Arch. f. exper. Path. u. Pharmacol. **100**:93-111, 1923.



was absent at pressures below 10 mm. of mercury. It usually began at pressures varying between 10 and 15 mm., the critical pressure for that segment of bowel (fig. 2).

With increasing distention the peristaltic waves were usually augmented in size until a pressure varying between 15 and 30 mm. of mercury was reached.

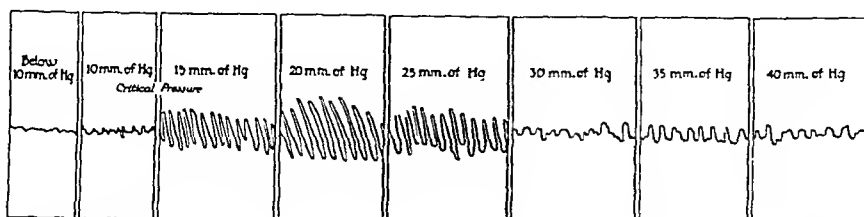


Fig. 2.—Effect of increased intraenteric pressure on peristalsis of the ileum.

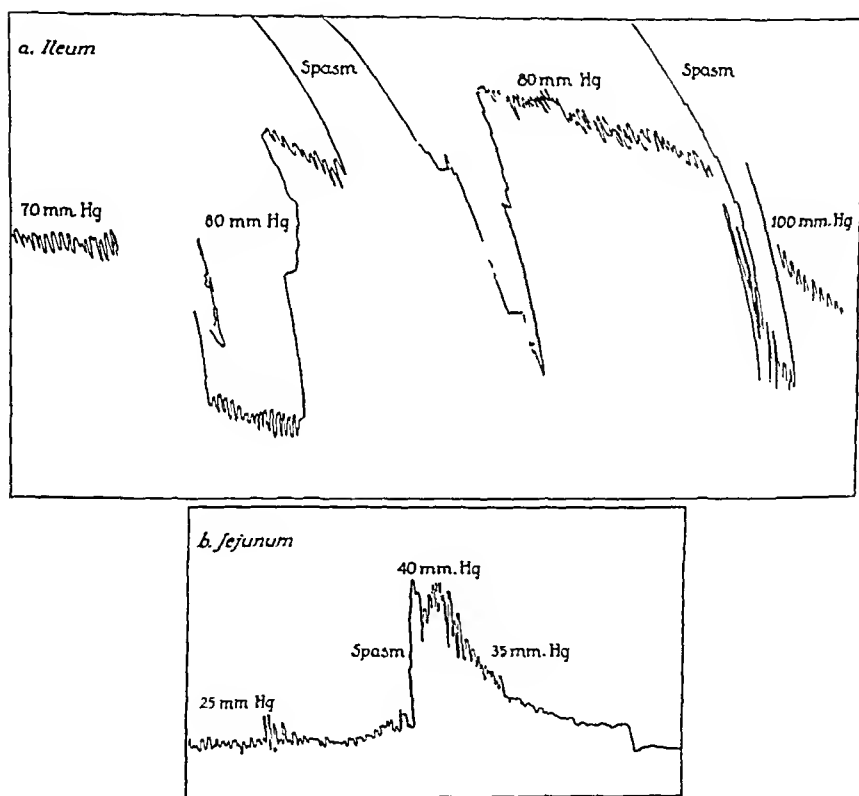


Fig. 3.—Spasm induced by increased intraenteric pressure.

After a pressure of 30 mm. of mercury was reached there was no further increase in the size of the peristaltic waves.

When intestinal loops were subjected to pressures varying between 40 and 80 mm. of mercury for sixty minutes or more, spasmodic contractions of the bowel similar to those occurring in the clinical subjects, that is, to intermittent colic, were occasionally seen (fig. 3). This, however, was not a constant finding. With the animal under light anesthesia, these contractions were accompanied by evidence of pain.

In a jejunal loop, such spasmodic contraction of the bowel was produced with a much lower pressure, that is, 25 mm. of mercury for one hour. During the violent contractions of the bowel, the pressure within the lumen was raised from 25 to 40 mm. of mercury (fig. 3).

To determine the optimal intraenteric pressure for peristalsis, the pressure in the loop of jejunum was gradually increased to 45 mm. of mercury by injecting fluid into the lumen of the bowel. When the tube was clamped, the pressure gradually decreased as the walls of the bowel relaxed. It was noted that with the decrease in pressure peristalsis was at first increased, reaching a maximum at a pressure of 20 mm. of mercury, and then decreased with further diminution in pressure.

*Effect of Sudden Decompression of the Bowel on Peristalsis.*—When a loop of bowel which had been subjected to increased intraenteric pressure was suddenly decompressed, it responded with violent peristalsis (fig. 4). Loops of ileum subjected to a pressure varying between 40 and 100 mm. of mercury for thirty to sixty minutes responded with violent peristalsis when suddenly emptied. One of these loops very rapidly built its pressure up to 40 mm. of mercury and showed violent peristaltic waves. The rapid increase in tone and augmentation of peristalsis

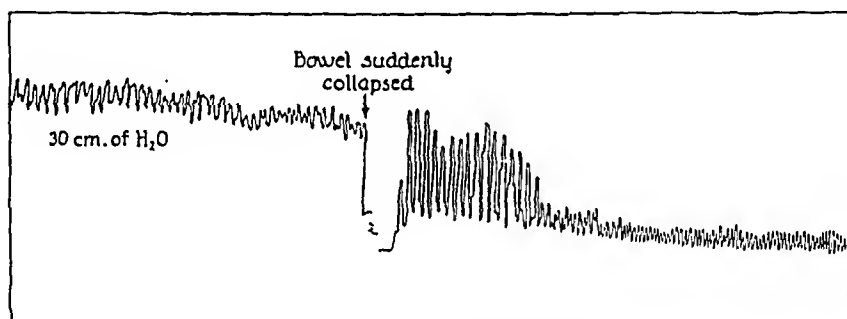


Fig. 4.—Effect of sudden decompression of the ileum on peristalsis.

are the usual reaction of the normal viable bowel to decompression. It is conceivable that if the distention of the intestine were maintained long enough to interfere with its viability the bowel would not respond in this manner. This was noted when pathologic changes (necrosis) occurred owing to prolonged distention. When a loop of ileum which had been subjected to simple obstruction for forty-eight hours was distended to a pressure of 60 mm. of mercury for one hour and then suddenly decompressed, no increased peristalsis was noted.

*Relation of Postural Tone to Distention.*—It is well known that when hollow viscera are distended the walls of these organs relax and the pressure is gradually reduced. Sherrington<sup>18</sup> has referred to this phenomenon as "postural tone."

The tone of the intestinal musculature is apparently more important than the volume of the intestinal content in affecting peristalsis and intraenteric pressure. The increased pressure is dependent to a greater

18. Sherrington, C. S.: Postural Activity of Muscle and Nerve, *Brain* 38:191-234, 1915.

degree on the response of the intestinal musculature to the distention incident to stasis than on simple increase of content. It was noted that at a pressure of 25 mm. of mercury, with active peristalsis in the jejunum, aspiration of 10 cc. from the ileal loop had no effect on the pressure. Apparently changes in tone make up for small changes in volume. This conforms with the law of postural tone as postulated by Sherrington. Massive reduction of volume, that is, sudden decompression, results, however, in a lowering of the pressure. This is accompanied by a great increase in tone, as evidenced by the violent peristalsis and the consequent rapid increase of intraluminary pressure when distended loops of bowel are rapidly decompressed.

No doubt some degree of protection is afforded the wall of the bowel by its ability to dilate and to accommodate itself to increased tension. There is a progressive increase in its diameter in proportion to the duration of the obstruction; that is, the diameter of bowel obstructed for a period of ninety-six hours is greater than that of bowel obstructed for only twenty-four hours. This increase is due in part to stretching caused by the increased intraenteric pressure, but it is principally due to relaxation of the intestinal musculature. The tension on any part of the intestine is dependent on its circumference and on the intraenteric pressure. It is well known that after complete obstruction of the left half of the colon perforation of the bowel is observed most frequently in the cecum. This may be due to the fact that, having the greatest lumen, it is subjected to the greatest pressure.

Sustained high pressure is more damaging to the bowel than intermittent pressure, even if the latter is of so high a degree as to cause local blanching. Ample opportunity is afforded the bowel to dilate and to return to its normal state in the interval between contractions. This pressure-free interval is lacking, of course, when the intraenteric pressure is sustained at a constant level. The insignificant histologic changes observed in experimental and clinical cases of simple intestinal obstruction may be accounted for by this ability of the bowel to relax and so accommodate itself to elevated tension. This phenomenon of relaxation undoubtedly also occurs to some degree in closed intestinal loops, but it is evident that sooner or later the elevated pressure must become constant, bringing with it the danger of strangulation.

#### EFFECT OF DISTENTION ON INTESTINAL SECRETION

Enderlen and Hotz<sup>19</sup> in 1911 noted that in the later stages of obstruction there was extravasation of fluid into the bowel. More

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19. Enderlen, E., and Hotz, G.: Ueber die Resorption bei Ileus und Peritonitis, Mitt. a. d. Grenzgeb. d. Med. u. Chir. 23:755, 1911.

recently Herrin and Meek,<sup>20</sup> working with various types of intestinal fistulas, obtained a tremendous increase in secretion by distending the pouches with balloons at a tension of 80 mm. of mercury. They obtained as much as 550 cc. in twenty-four hours from a pouch 20 cm. in length. They stated: "Distention is a strong stimulus to intestinal secretion, and in obstruction this must work in a vicious cycle." This increase in secretion may be brought about in two ways:

1. By some nervous reflex mechanism whereby, as a result of the increased activity incident to distention, glandular secretion is increased by stimulation through Auerbach's plexus.

2. By increase in capillary permeability. It has been shown by Landis<sup>21</sup> that increase of capillary pressure results in increased permeability of the capillary wall. Experimentally, stasis of blood also increases the permeability of the capillary wall, so that at first a protein-free filtrate and later a protein-containing filtrate passes out of the blood vessels into the tissue spaces. Both increased intracapillary pressure and stasis of blood occur in simple intestinal obstruction. From the capillaries in the mucosa fluid passes into the lumen of the bowel, and from the serosa fluid passes into the peritoneal cavity. With active peristalsis sufficiently strong to result in local anemia of the intestine, fluid may actually be squeezed out of the capillaries.

Burget<sup>4</sup> in 1930 noted that the severity of symptoms in dogs with closed loop obstructions varied directly with the degree of distention of the loops. If the distention was allowed to increase, anorexia, vomiting and dehydration appeared. Relief of distention by aspiration of the contents of the loops at once relieved the symptoms. Herrin and Meek<sup>20</sup> have recently demonstrated that a nervous cause is largely responsible for this train of events. Dogs were able to withstand distention of denervated loops of bowel indefinitely. They did not lose their appetites and were able to maintain the level of their blood chlorides in spite of an abnormal loss of fluid and electrolytes from the distended ileal loops. Dogs in which the nerve supply of the bowel was not interfered with died showing the clinical picture of high intestinal obstruction—that is, dechlorination of the tissues and of the blood, and dehydration.

The degree to which this increased amount of fluid in the bowel contributes to distention is dependent on the level of obstruction. With high obstruction, when the fluid is evacuated early by vomiting, the distention is much less than when the obstruction is in the lower part

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20. Herrin, R. C., and Meek, W. J.: Distention as a Factor in Intestinal Obstruction, *Arch. Int. Med.* **51**:152-168 (Jan.) 1933.

21. Landis, E. M.: Micro-Injection Studies of Capillary Permeability: The Effect of Lack of Oxygen on the Permeability of the Capillary Wall to Fluid and to Plasma Protein, *Am. J. Physiol.* **83**:528-542. 1928.

of the ileum. In low ileal obstruction, especially in obstruction of the closed loop type which occurs in the colon because of the competent ileocecal sphincter, the bowel cannot decompress itself by reversed peristalsis and regurgitation; thus, the increased secretion results in progressive augmentation of the distention.

Under the influence of obstruction, the total amount of fluid in the lumen of the bowel is increased by the response of the intestine to distention. Since the intestine fails to reabsorb this fluid, the cause of dehydration is apparent.

#### INFLUENCE OF OBSTRUCTION AND INCREASED INTRAENTERIC PRESSURE ON INTESTINAL ABSORPTION

It is generally conceded that the contents of both the obstructed and the normal bowel are toxic if injected intravenously. The manner and the routes of toxic absorption from the obstructed bowel are still subjects of considerable speculation and debate. The possible avenues by which toxic material of any kind may be absorbed are (1) the mesenteric veins, (2) the lymphatics and (3) the intestinal wall (transperitoneally by diffusion).

*Venous Absorption.*—Decreased absorption through the mesenteric veins of such substances as dextrose, salt, iodide, strychnine and histamine has been observed by many investigators. It is remotely possible, however, that the factor of selective absorption may play a role in determining the degree of absorption through the veins in simple intestinal obstruction. It may be that the bowel in a condition of obstruction becomes permeable to a toxin which is different from any of the substances used in experiments on animals.

This decrease of absorption, both quantitative and qualitative, has been attributed to the increase of intraenteric pressure which occurs in intestinal obstruction. Gatch and Culbertson<sup>22</sup> have investigated the absorption of specific substances, such as bromides and alcohol, from the normal bowel under moderately increased intraenteric pressure. They found that for pressures between 10 mm. of mercury and the diastolic blood pressure of the animals used in the experiments the rate of absorption of these substances is relatively constant.

The deleterious effect of simple ileal obstruction on the absorption of water from loops of ileum is illustrated by the fact that under identical experimental conditions closed loops of normal ileum absorbed approximately 90 per cent of the amount of water necessary to fill them, while loops of ileum which had been subjected to previous obstruction were able to absorb less than 10 per cent (table 11).

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22. Gatch, W. D., and Culbertson, C. G.: Circulatory Disturbances Caused by Intestinal Obstruction, *Ann. Surg.* 102:619-635, 1935.

Absorption of Water from the Normal and from the Obstructed Ileum at Various Levels of Increased Pressure: There is little information available on the effects of relatively low intraenteric pressure, such as exists in experimental and clinical intestinal obstruction on absorption either from the normal or from the obstructed bowel. To supply these data the following experiments were undertaken:

In 41 normal dogs the amount of water absorbed from equal-sized loops of the lower portion of the ileum under the influence of a pressure of 10 to 100 cm. of water for one hour was determined. In this series of experiments on normal dogs it was found that a pressure of 40 cm. of water was the optimal pressure for absorption and that increase of pressure above that level resulted in lowering of the absorption ratio (table 12). A pressure of 40 cm. of water is equivalent to a pressure of about 3 cm. of mercury, which pressure Van Zwahlenberg<sup>23</sup> has shown to be the level at which the circulation of the intestinal wall begins to be impaired.

TABLE 11.—*Absorption of Water from the Normal and from the Obstructed Ileum*

Dog	Weight, Lb.	Amount Injected, Cc.	Amount Absorbed, Cc.	Percentage Absorbed
1 (normal).....	44	50	47	94.0
2 (normal).....	41	50	26	86.6
3 (normal).....	23	50	42	84.0
4 (normal).....	54	40	33	82.5
Average normal.....				86.7
5 (with obstruction).....	19	60	5	8.3
6 (with obstruction).....	14	60	6	10.0
Average with obstruction.....				9.0

The time factor period of observation (one hour) in these experiments is most important, because when a pressure of 40 cm. of water was sustained over a considerably longer period (seventeen hours) definite pathologic changes in the wall of the bowel occurred. No such changes could be demonstrated in the intestinal wall after distention by a pressure of 40 cm. of water for one hour.

In a series of experiments on dogs with simple ileal obstruction of forty-eight hours' duration, a similar result was obtained; 40 cm. of water was the optimal pressure for absorption, but with higher pressures the decrease in absorption was more marked than in the series of experiments on normal dogs (table 13).

There was a significant decrease in absorption of water from the obstructed ileum as compared with its absorption from the normal ileum, varying between 20 to 60 cm. of water (table 14 and fig. 5). There was no significant difference between the two groups in the amount of water absorbed at a pressure of 10 cm. Pressures above 80 cm. of water were not utilized in this series because at these higher levels of pressure tearing of the serosa and leakage of the intestinal contents occurred.

23. Van Zwahlenberg, C.: Strangulation Resulting from Distention of the Hollow Viscera: Its Bearing upon Appendicitis, Strangulated Hernia and Gall Bladder Disease. *Ann. Surg.* 46:780-786, 1907..

This amount of pressure (40 cm.) is of course the optimal level for the absorption of water only for the particular segment of the bowel investigated (the lower part of the ileum). From the work of

TABLE 12.—*Effect of Increased Intracenteric Pressure on Absorption of Water from Loops of Normal Ileum*

	Dog	Weight, Kg.	Amount Absorbed, Cc.	Ratio, Cc. per Kg. per Hour
10 cm. water	1.....	15.0	100	6.6
	2.....	22.7	105	4.6
	3.....	26.4	165	6.2
	4.....	26.4	125	4.7
	5.....	12.3	70	5.7
	6.....	15.0	95	6.3
	7.....	19.5	115	5.9
	8.....	16.5	70	4.2
	Average ratio at 10 cm.....			5.5
20 cm. water	9.....	20.4	236	11.5
	10.....	20.9	190	9.1
	11.....	14.1	180	12.7
	12.....	13.2	120	9.1
	13.....	15.4	180	8.8
	14.....	9.1	125	13.7
	15.....	7.3	60	8.2
	16.....	12.7	160	12.6
	17.....	11.4	100	8.8
	Average ratio at 20 cm.....			10.5
40 cm. water	18.....	19.1	285	14.9
	19.....	14.1	170	12.1
	20.....	10.0	150	15.0
	21.....	12.4	130	10.5
	22.....	17.7	190	10.7
	23.....	9.1	110	12.1
	24.....	8.6	115	13.4
	Average ratio at 40 cm.....			12.7
60 cm. water	25.....	20.5	210	10.2
	26.....	17.3	125	7.2
	27.....	12.7	160	12.6
	28.....	20.5	150	7.3
	29.....	10.0	95	9.5
	30.....	12.3	120	9.7
	Average ratio at 60 cm.....			9.4
80 cm. water	31.....	6.8	55	8.1
	32.....	9.5	50	5.3
	33.....	9.5	70	7.4
	34.....	15.0	50	3.3
	35.....	18.2	120	6.6
	Average ratio at 80 cm.....			6.1
100 cm. water	36.....	11.4	55	4.8
	37.....	12.3	35	2.8
	38.....	14.5	72	4.9
	39.....	17.3	105	6.0
	40.....	11.8	75	6.3
	Average ratio at 100 cm.....			4.9

Dragstedt,<sup>24</sup> it may be surmised that the optimal level is lower in the jejunum and higher in the proximal portion of the colon, as he has

24. Dragstedt, C. A.; Lang, V. F., and Millet, R. F.: Relative Effects of Distention on Different Portions of the Intestine, Arch. Surg. **18**:2257-2263 (June) 1929.

shown that from the jejunum to the colon a correspondingly higher intraenteric pressure is necessary to interfere with circulation to the wall of the bowel.

TABLE 13.—*Effect of Increased Intraenteric Pressure on Absorption of Water from Loops of Obstructed Ileum*

	Dog	Weight, Kg.	Amount Absorbed, Cc.	Ratio, Cc. per Kg. per Hour
10 cm. water	1.....	13.4	100	7.5
	2.....	11.6	100	8.6
	3.....	19.5	110	5.6
	4.....	16.9	80	4.7
	5.....	16.4	75	4.6
Average ratio at 10 cm.....				6.2
20 cm. water	6.....	32.5	170	5.3
	7.....	20.0	150	7.5
	8.....	19.5	200	10.2
	9.....	19.5	80	4.1
	10.....	9.1	55	6.0
Average ratio at 20 cm.....				6.6
40 cm. water	11.....	15.0	160	10.6
	12.....	20.0	190	9.5
	13.....	14.1	160	11.3
	14.....	15.0	150	10.0
Average ratio at 40 cm.....				10.4
60 cm. water	15.....	13.2	82	6.2
	16.....	17.3	55	3.2
	17.....	28.6	155	5.3
	18.....	21.8	85	3.9
	19.....	23.2	85	3.7
Average ratio at 60 cm.....				4.4
80 cm. water	20.....	12.0	50	4.1
	21.....	20.5	55	2.7
	22.....	21.0	30	1.4
	23.....	21.0	30	1.4
	24.....	10.1	35	3.3
	25.....	14.0	20	1.5
Average ratio at 80 cm.....				2.4

TABLE 14.—*Comparison of Effect of Obstruction of the Ileum on the Absorption Ratio, by Fisher's Method*

Pressure	Ratio		Differences	t	P
	Normal	Obstructed			
10 cm.	5.53	6.20	+0.67	0.92	0.40
20 cm.	10.5	6.62	-3.88	3.18	<0.01
40 cm.	12.67	10.35	-2.32	2.37	0.05
60 cm.	9.42	4.46	-4.96	4.77	<0.01
80 cm.	6.14	2.4	-3.74	1.28	0.20

These findings are in agreement with those of early workers, Hamburger<sup>25</sup> and Leubuscher,<sup>26</sup> on the effect of intrainestinal pressure

25. Hamburger, H. J., cited by Goldschmidt, S.: On the Mechanism of Absorption from the Intestine, *Physiol. Rev.* 1:421-453, 1921.

26. Leubuscher, cited by Goldschmidt, S.: On the Mechanism of Absorption from the Intestine, *Physiol. Rev.* 1:421-453, 1921.



on intestinal absorption. Leubuscher ascribed the primary increase of absorption to unfolding of the mucosa and the secondary decrease to interference with the blood supply. Wells<sup>27</sup> found that the absorption of saline solution from closed loops was in direct proportion to the intraenteric pressure. However, his studies include pressures only up to 16 cm. of water. Elman and Aird,<sup>6</sup> in two experiments on animals and in one observation on a human being, showed essentially the same result which was obtained in these experiments. They noted maximum absorption at 50 cm. of water. At higher pressures (85 to 90 cm. of water), absorption did not take place. In their single experiment on a human being, the maximum absorption occurred at a pressure of

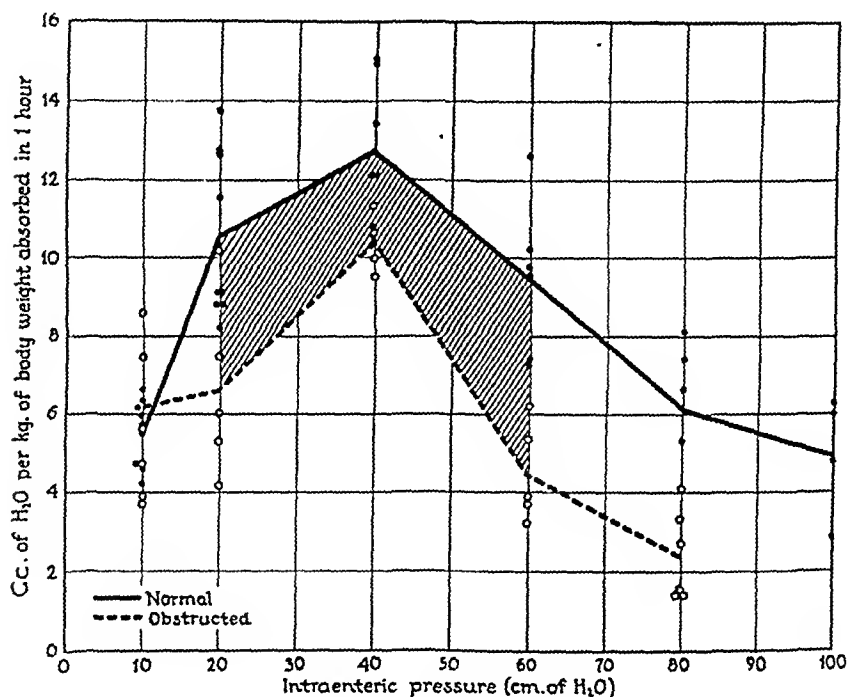


Fig. 5.—Effect of increased intraenteric pressure on the absorption of water from the normal and from the obstructed ileum. The shaded areas indicate significant difference between means.

40 cm. of water and fell progressively on increase of pressure until at a pressure of 70 cm. of water definite secretion into the loop occurred.

**Absorption of Strychnine from the Normal and From the Obstructed Ileum:** Though the avenues by which absorption may occur in obstruction are known, it is extremely difficult to ascertain definitely through

27. Wells, H. S.: Passage of Materials Through Intestinal Wall: Relation Between Intra-Intestinal Pressure and the Rate of Absorption of Water, *Am. J. Physiol.* 99:209-220, 1931.

which avenue and to what degree toxic absorption, if any, takes place. It is possible by the employment of such substances as strychnine and organic dyes and by the elimination of certain of the avenues for absorption to gain some information on this subject.

Strychnine was absorbed directly from the peritoneal cavity of the cat in two minutes and from the loops of the normal ileum of the cat in three minutes. In animals with intestinal obstruction a slight but definite delay in absorption from the bowel was evident within the first twenty-four hours of obstruction; that is, three to six minutes were required for absorption as compared with two to three minutes in the normal intestine. This increase of absorption time was more marked when the loops were outside the peritoneal cavity (eight to thirteen minutes). The absorption time seemed to increase directly with the duration of the obstruction.

Absorption of strychnine takes place very rapidly through the mesentery even when the loop is outside the peritoneal cavity. The comparatively slight increase of absorption time in obstructed loops in the extraperitoneal position is due to the abnormal location of the loop, to slight tension on the mesentery, to handling of the bowel or to changes of temperature which must occur despite attempts to maintain normal conditions. It appears that the obstructed bowel is more sensitive to such changes than is the normal bowel.

**Influence of Increased Intraenteric Pressure on the Absorption of Strychnine from the Normal and from the Obstructed Ileum:** To determine the level of intraenteric pressure which prevents intestinal absorption, experiments similar to those of Gatch<sup>28</sup> were carried out. With a constant pressure of more than 100 mm. of mercury, absorption of strychnine could not be demonstrated during several hours of observation. Only when the intraenteric pressure was reduced to approximately 70 mm. of mercury could the absorption of strychnine be shown. This occurred regardless of the peritoneal or extraperitoneal location of the loop, indicating that absorption took place by way of the mesentery. Two dogs with simple low ileal obstruction of three days' duration showed symptoms of absorption of strychnine at pressures of 50 and 60 mm. of mercury respectively when this experiment was carried out.

When strychnine was introduced into a loop a pressure of 100 mm. of mercury and the abdomen was closed, convulsions did not develop until the intraenteric pressure was decreased by relaxation of the bowel to a pressure of 75 mm. of mercury, at which critical point the strychnine was absorbed via the veins of the mesentery.

It is concluded from these experiments that an intraenteric pressure of more than 75 mm. of mercury prevents the mesenteric absorption of strychnine.

It has been shown that absorption of strychnine via the mesenteric veins is less in simple ileal obstruction than under normal conditions.

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28. Gatch, W. D.; Owen, J. E., and Trusler, H. M.: The Effect of Distention of the Bowel upon Its Circulation and upon Absorption from Its Lumen, *West. J. Surg.* 40:161-167, 1932.

The obstructed bowel absorbs only a fraction of the amount of water taken up by a similar segment of normal intestine under identical experimental conditions. Increase of the intraintestinal pressure results in a progressive increase in the absorption of water from the normal bowel until a pressure of 40 cm. of water is reached. Higher pressures produce a fall of the rate of absorption to below the normal rate. The same holds true, but to a lesser degree, in the obstructed bowel. Pressures above 75 mm. of mercury effectively prevent venous absorption.

*Lymphatic Absorption.*—An attempt was made to determine the occurrence of lymphatic absorption in simple intestinal obstruction and with increased intraenteric pressures.<sup>29</sup>

*Absorption of Dyes Via the Lymphatics in Simple Ileal Obstruction:* Fifteen normal cats were given trypan blue by stomach tube and 5 by enteral injections. In none was the dye visible in the regional lymph nodes at intervals of two to forty-eight hours. When cats with simple ileal obstruction were given the dye by stomach tube none appeared in the lymphatics. When this dye was injected into the bowel at the time the obstruction was produced, 3 of 8 cats showed colored nodes. When intestinal stasis was induced by chemical peritonitis (with iodine) 1 of 5 cats showed blue lymph nodes.

*Absorption of Dyes from the Lumen of the Intestine Under Increased Intraenteric Pressure:* Closed ileal loops were prepared in 12 cats and the loops distended with dye until the walls became tense (marked increase of intraenteric pressure). Ten of the 12 cats at autopsy (twenty-four to seventy-two hours) showed blue nodes. In several of these experiments the dye, as it was injected into the lumen of the bowel under pressure, could be seen to enter Peyer's patches after five or ten minutes and subsequently to enter the lymph vessels of the mesentery. This procedure was repeated in vitro with fresh excised viable segments of normal and obstructed bowel of the cat, with the following results: Pressures of 100 mm. of mercury in a normal loop forced the dye out into the lymphatics in five minutes. In another normal loop a pressure of 50 mm. of mercury forced the dye into the lymph vessels in one hour. When a fresh viable loop excised from a cat with simple ileal obstruction of forty-eight hours' duration was subjected to a pressure of 40 mm. of mercury, dye appeared in the lymph vessels in thirty minutes. When nonviable loops were subjected to increased intraenteric pressure, the dye, in addition to being forced rapidly into the lymphatics, permeated the wall of the intestine directly (table 15).

*Absorption of Bacteria Via the Lymphatics:* The absorption of bacteria through the lymphatics was studied in the following manner: A heavy suspension of *Bacillus pyocyaneus* was injected into the ileums of 6 normal cats. Preliminary cultures of regional lymph nodes were sterile. Cultures of material taken from the nodes one hour after the intraenteric injection showed *B. pyocyaneus* in 2 cases and failed to do so in 4; in 2 of the latter, cultures of *B. pyocyaneus* were obtained when the cats were again operated on after twenty-four hours. In 2 additional cats in which the bacterial suspension was introduced into closed loops

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29. Sperling, L., and Wangenstein, O. H.: Lymphatic Absorption in Simple Obstruction: Significance of Distention upon Its Occurrence, *Proc. Soc. Exper. Biol. & Med.* **33**:22-26, 1935.

under pressure for one hour, cultures of material taken from the regional lymph nodes produced *B. pyocyaneus*.

Similar experiments were carried out in normal dogs and in dogs with intestinal obstruction. Cultures of *B. pyocyaneus* were obtained in material from the regional lymph nodes in 2 of 9 experiments on normal dogs and in all of 6 experiments performed on dogs with low ileal obstruction of twenty-four to ninety-six hours' duration. Control cultures of material taken from the lymph nodes before the injection of the bacterial suspension failed in every case to show *B. pyocyaneus*. Cultures of the lymph in the thoracic ducts of 5 normal dogs and of 6 dogs with intestinal obstruction proved entirely sterile. Cultures of blood from the femoral veins and from the mesenteric vein draining the obstructed bowel were all sterile.

In the experiments on the absorption of dyes, the lymph nodes of the animals with closed ileal loops were stained more deeply than those of the animals with simple ileal obstruction. The percentage of colored nodes was higher in the group with closed loops than in that with simple ileal obstruction. This is probably due to the fact that a higher intra-enteric pressure is developed in the closed loop.

TABLE 15.—*Effects of Distention on Lymphatic Absorption and Transperitoneal Passage of Dyes in Excised Loops of Normal and Obstructed Ileum in Cats*

Time After Death, Hr.	Obstruction, Hr.	Pressure, Mm. Hg	Viability	Dye in Lymph Nodes After Min.	Permeability of Bowel Wall After Min.
0	None	100	Viable	5	Negative, 60
0	None	50	Viable	60	Negative, 60
0	24	130	Viable	10	Negative, 60
0	48	40	Viable	30	Negative, 60
6	24	100	None	5	Positive, 15
8	48	100	None	10	Positive, 30

In the control experiments the absorption of dye into the lymphatics is without doubt prevented by its rapid transport through the bowel. Transport, of course, does not take place in circumstances of obstruction. In its stead there are stasis, distention and increased intraenteric pressure.

The results of these experiments are in accord with the well known physiologic principle that increase of venous pressure enhances lymphatic flow. In the closed loop type of obstruction the increased tension in the bowel produces increased venous pressure. The appearance of dyes in the lymphatics of cats dying of simple intestinal obstruction and the failure to demonstrate the dye in the lymphatics of animals with simple intestinal obstruction that were killed may be explained by the fact, as was demonstrated by Bainbridge,<sup>30</sup> that the flow of lymph continues after death. From these experiments it is apparent that a

30. Bainbridge, F. A.: Postmortem Flow of Lymph, *J. Physiol.* **34**:275-281, 1906.

high correlation exists between the increased intraenteric pressure in obstruction and the degree of lymphatic absorption.

It appears that the regional lymph nodes normally serve as an effective barrier against the overwhelming absorption of bacteria into the blood stream via the mesenteric lymphatic channels. True bacteremia probably does not occur and is probably not the cause of death in uncomplicated intestinal obstruction, as cultures producing the test organism could not be obtained in material taken from the thoracic duct. The lymph nodes yielding the organisms acted as efficient barriers and prevented centripetal invasion. Toxemia of bacterial origin or from lymphatic absorption of toxic amines from the bowel, however, has not been wholly excluded.

**Significance of Lymphatic Absorption in Simple Intestinal Obstruction:** An attempt was made to evaluate the significance of lymphatic absorption in the lethal issue of simple intestinal obstruction by interruption of the lymphatic channels. This was accomplished by ligating and cutting the lymphatic pedicle of the mesenteries in 4 cats after the establishment of simple ileal obstruction. The period of survival was not greater than that of the control animals, in which the lymphatic pedicle was not severed.

These observations seem to justify the conclusion that intestinal obstruction and increased intraenteric pressure increased the absorption of dyes and of bacteria into the regional lymph nodes. No evidence was, however, adduced to indicate that this occurrence is of great significance in the lethal issue of simple intestinal obstruction in animals.

**Transperitoneal Absorption.**—The wall of the normal viable bowel is resistant to the passage of toxic material from its lumen into the peritoneal cavity. Most investigators are agreed that transperitoneal passage of any material does not take place unless extreme increases of intrainestinal pressure obtain or unless gross injury to the bowel wall is present. Schönbauer,<sup>31</sup> Gatch,<sup>28</sup> Chenuth,<sup>32</sup> and others have advanced the hypothesis that death following intestinal obstruction is due to the absorption of toxins which have passed through the wall of the bowel into the peritoneal cavity.

Stone and Firor,<sup>5</sup> Gatch,<sup>28</sup> Dobyns and Dragstedt<sup>33</sup> and others have indicated that increased intraenteric pressure may force toxic materials through the intestinal wall. Gatch's work on the permeability of the bowel to hydrocyanic acid under increased tension was repeated

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31. Schönbauer, L.: Die Fermente in ihrer Beziehung zu gewissen Erkrankungen der Gallenblase und zum Ileus, *Arch. f. klin. Chir.* **130**:427-462, 1924.

32. Chenuth, A.: L'experimentation dans l'occlusion mechanique du jejunum, *Rev. de chir., Paris* **64**:474-834, 1926.

33. Dobyns, G. J., and Dragstedt, C. A.: Intra-Intestinal Pressure and Absorption from the Intestine, *Proc. Soc. Exper. Biol. & Med.* **30**:707-709, 1933.

and confirmed.<sup>34</sup> Apparently, however, the wall of the viable bowel is permeable by simple chemical compounds only, as Gatch was unable to show transperitoneal absorption of nicotine. The passage of strychnine through the wall of the viable bowel could not be demonstrated even with marked increase of intrainestinal pressure.

**Passage of Strychnine Through the Wall of the Devascularized Bowel and Through Devascularized Bowel Which Had Previously Been Subjected to Simple Ileal Obstruction:** In 4 cats with simple ileal obstruction of ninety-six hours' duration and in 1 cat with simple ileal obstruction of one hundred and forty-four hours' duration, the distal 3 inches (7.5 cm.) of the obstructed intestine was devascularized and a large dose of strychnine (10 to 50 mg.) was injected into the lumen of this segment. Similar devascularized loops were prepared in 5 normal cats. After closure of the abdomen, the cats were revived and were observed for signs of absorption of the poison. The animals with ileal obstruction showed convulsive signs within two and one-half or three hours and were dead within three or four hours. The normal cats did not show signs of poisoning until from four and one-half to seven hours had elapsed.

**Effect of Increased Intrainestinal Pressure on the Passage of Strychnine Through the Wall of the Devascularized Bowel and Through the Bowel Which Had Previously Been Subjected to Simple Ileal Obstruction:** Closed loops of ileum 10 inches (25 cm.) in length were prepared in 4 normal dogs. The loops were devascularized, and 50 mg. of strychnine was introduced into the lumens. Two of the loops were distended with air to a pressure above 100 mm. of mercury; 2 others were not distended. The dogs were revived and were observed carefully for signs of strychnine poisoning. The dogs with ileal loops under increased pressure had convulsions within three hours. Those in which the ileal loops were not under pressure remained free from symptoms for more than eight hours.

In 3 dogs with simple ileal obstruction of five days' duration closed loops of ileum were prepared just above the site of obstruction. The intraenteric pressure was raised to approximately 120 mm. of mercury, and 50 mg. of strychnine was introduced into the lumen of the closed loop. One dog showed signs of strychnine poisoning within eighteen minutes. The second dog had symptoms within forty-five minutes. The third dog showed no symptoms after seventy-five minutes. Examination revealed numerous rents in the serosa in all 3 cases. The obstructed bowel cannot tolerate great increases of intraenteric pressure for any considerable time. In all of the experiments in which obstructed bowel was utilized and subjected to a pressure of 80 mm. of mercury or more for one hour, there developed rents on the antimesenteric border which might facilitate transperitoneal passage of poisons or toxins.

**Effect of Increased Intraenteric Pressure on the Passage of Dyes Through the Wall of the Bowel:** Freshly excised viable loops of ileum were obtained immediately after death from 2 normal cats killed during other experiments.<sup>34</sup> The loops were filled with a 1 per cent solution of trypan blue and subjected to 50 and 100 mm. of mercury of pressure, respectively, for one hour. Freshly excised loops from 2 cats with an antecedent low ileal obstruction of twenty-four and forty-eight hours' duration, respectively, were filled with dye and subjected to distention

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34. Sperling, L., and Wangenstein, O. H.: Transperitoneal Absorption: VI. The Significance of Impaired Viability and the Influence of Distention on Its Occurrence, *Proc. Soc. Exper. Biol. & Med.* **32**:1385-1389, 1935.

at respective pressures of 40 and 130 mm. of mercury. The dye had not permeated the bowel after one hour of distention. However, when ileal loops from 2 cats with intestinal obstruction, dead six and eight hours respectively, were subjected to distention at a pressure of 100 mm. of mercury, the nonviable bowel permitted the dye to pass directly through its wall in fifteen to thirty minutes. When a 1 per cent solution of gentian violet was injected into the intestinal lumen in cats with simple obstruction and obstruction of the closed loop type, only a slight staining of the mucosa was present in a few instances on microscopic section of the bowel (Churchman's method<sup>35</sup>). As this was not a constant finding and was present only in cats dead several hours, it was assumed that the penetration of the mucosa was a postmortem phenomenon. In none of the cats could transperitoneal passage of the dye be demonstrated by wrapping gauze about the outside of the bowel. In 1 experiment the dye was introduced into the loop under high pressure so that the loop was very tense. When the cat was killed seventy-two hours later (moribund), several purple spots were visible on the antimesenteric border. These were judged to be nonviable necrotic areas through which the dye had passed.

**Correlation of the Viability of the Intestinal Wall with Its Permeability in Simple Ileal Obstruction:** The following experiments were undertaken to determine whether any correlation exists between the permeability and the viability of the bowel in simple ileal obstruction.

Fifteen cats with simple ileal obstruction of six to one hundred and sixty-eight hours' duration were killed at definite intervals after the obstruction, and the viability and permeability of the loops were noted in the following manner: The terminal 4 inches (10 cm.) of the obstructed bowel was removed, and the closed segment was at once immersed in a beaker of Ringer's solution (temperature 37 C.). The viability of the segment was determined by noting the length of time during which it reacted by contraction to a measured electrical stimulus repeated every fifteen minutes. The loop was considered to have lost its viability when no contraction appeared after prolonged stimulation. Permeability of the bowel was determined by immersing the segments, filled with potassium ferrocyanide, at intervals of fifteen minutes into another beaker of Ringer's solution, containing ferric chloride, and noting the time at which the characteristic prussian blue color appeared.

The segments of bowel from the cats with intestinal obstruction were all viable and showed no permeability when first removed. They remained viable for periods varying between fifteen minutes to one and one-quarter hours after the animals were killed. Most specimens resisted permeation for some time after some impairment of viability was evident. The segments from the dead cats which had been normal and from cats already dead of intestinal obstruction were of course nonviable and showed immediate permeation. Loops obstructed for ninety-six hours or longer showed signs of impairment of viability (table 16).

In a similar study, Schempp<sup>36</sup> could not find any definite relation between the duration of obstruction and the viability of the bowel.

That a real difference in permeability and viability exists between normal bowel and obstructed bowel is shown by experiments on the

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35. Churchman, J. W.: The Selective Bacteriostatic Action of Gentian Violet and Other Dyes, *J. Urol.* **11**:1-18, 1924.

36. Schempp, E.: Zur Frage der Durchlässigkeit der Darmwand für gelöste Stoff, insbesondere beim Darmverschluss, *Beitr. z. klin. Chir.* **143**:728-736, 1928.

permeability of devascularized loops by strychnine. Obstructed devascularized loops become permeable in two and one-half or three hours, while the normal loops resist permeation at least four hours. Under similar conditions of increased pressure, the bowel of dogs with intestinal obstruction becomes permeable somewhat earlier because of tearing of the serosa.

TABLE 16.—*Correlation of Viability of Intestinal Wall in Simple Ileal Obstruction with Its Permeability by Potassium Ferrocyanide*

Duration of Obstruction, Hr.	Viability Impaired After Min.	Viability Lost After Min.	Permeable After Min.
8 normal cats.....	30-75	30-150	15-55
6, 18, 18, 24.....	30-60	60-120	45-60
30, 36, 48, 48.....	30-50	45-75	15-60
72, 72.....	15-30	30-90	30-90
96.....	15	15	25
120.....	15	30	20
168.....	15	30	5
Normal loop for cat dead 8 hours.....			5
Loop 72 hours obstructed from cat dead 8 hours.....			6
Loop 96 hours obstructed from cat dead 8 hours.....			2

TABLE 17.—*Effect of Sustained Intraenteric Pressure on the Appearance, Permeability and Viability of the Ileum*

Dog	Pressure Applied, Cm.	Reoperated On, After Hr.	Results
1	10	28	Petechial hemorrhage; viable; not permeable
2	10	27	Petechial hemorrhage; hemorrhage into lumen; viable; not permeable
3	15	18	Congested; hemorrhage into lumen; early necrosis; viable; not permeable
4	20	10	Congested; viable; not permeable
		22	Congestion marked; impaired viability; not permeable
		25	Hemorrhagic peritoneal fluid; necrosis; nonviable; permeable
5	20	22	Congested; viable; not permeable
		32	Dog dead; gangrene and necrosis; nonviable; permeable
6	40	2	Negative; viable; not permeable
7	40	4	Hemorrhage; viable; not permeable
8	40	11	Congested; bloody peritoneal fluid; viable; not permeable
		17	Dog dead; areas of necrosis; nonviable; permeable
9	40	28	Necrosis; nonviable; permeable
10	40	20	Split serosa; gangrenous patch; nonviable; permeable
11	40	20	Necrosis; nonviable; permeable
12	40	20	Hemorrhagic areas; early necrosis; viable; not permeable
		24	Necrosis spreading; nonviable; not permeable
		30	Mucosal ulcers; nonviable; permeable

Results of experiments on diffusion of dyes through the wall of the bowel accord with those of experiments on absorption of strychnine, that is, viable bowel resists permeation and nonviable, or dead, bowel is readily permeable.

The work of Gatch,<sup>22</sup> Dragstedt<sup>33</sup> and others concerning the effect of increased intrainestinal pressure on absorption is substantiated. The greater potential for the occurrence of transperitoneal absorption in the obstructed bowel is well shown in the results accompanying devasculari-



zation of normal and previously obstructed bowel. Still, evidence of transperitoneal absorption does not ordinarily appear until there is anatomic evidence of damage to the wall of the intestine, as will be shown in some following experiments.

These observations appear to warrant the conclusion that transperitoneal absorption in simple intestinal obstruction may occur, but only through devitalized segments of bowel subjected to distention, and that the obstructed bowel under similar experimental conditions is more permeable to strychnine than is the normal bowel.

#### EFFECT OF PROLONGED DISTENTION ON THE STRUCTURE, VIABILITY AND PERMEABILITY OF THE WALL OF THE BOWEL

Any pathologic changes in the bowel as a consequence of increased intraenteric pressure must be secondary to the effect of this increased pressure on the circulation of the intestinal wall.

Kocher<sup>37</sup> was the first to recognize the significance of increased intraenteric pressure. Many American investigators have since referred to the obvious disturbance of circulation and consequent impairment of function of the intestine as a result of increased intraenteric pressure (Van Zwahlenberg,<sup>38</sup> Dragstedt,<sup>33</sup> Gatch and others).

Van Zwahlenberg<sup>39</sup> attempted to explain the pathologic changes occurring in intestinal obstruction on the basis of anoxemia of the wall of the bowel. According to his research, stasis of blood results in a decreased oxygen supply, which affords excellent opportunity for the development of infection and its sequelae, gangrene, necrosis and perforation of the intestinal wall. He cited experimental evidence presented by Burget and Visscher<sup>40</sup> to show that the bowel deprived of its blood supply uses up all available oxygen very rapidly. Bacteria, especially anaerobes and facultative anaerobes, grow well in asphyxiated tissue. There can be no doubt that partial asphyxia of the wall of the bowel, due to stasis of blood, occurs in simple intestinal obstruction.

The stagnant contents of obstructed loops form an excellent culture medium for the growth of bacteria. Thus, bacterial growth may invade the partially asphyxiated tissues of the bowel, with resulting pathologic

37. Kocher, T.: Ueber Ileus, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **4**:195-230, 1899.

38. Van Zwahlenberg, C.: Hydraulic Vicious Circle as It Develops in Intestine: Effect of Intra-Intestinal Pressure on the Pathology and Physiology of the Bowel, Am. J. Surg. **18**:104-112, 1932.

39. Van Zwahlenberg, C.: Hydraulic Vicious Circle as It Develops in Acute Appendicitis, Am. J. Surg. **16**:427-440, 1932.

40. Burget and Visscher, cited by Van Zwahlenberg, C.: Oxygen Lack in Hydraulic Vicious Circle, Am. J. Surg. **18**:133, 1932.

changes. Downey<sup>41</sup> in 1917 demonstrated that venous stasis is conducive to invasion by leukocytes. This would explain the infiltration of the bowel with polymorphonuclear and mononuclear cells which occurs when the intestine is subjected to prolonged distention. Thus, infiltration with leukocytes occurs first as a response to the invasion of the partially asphyxiated tissues by bacteria and second as a result of the stasis of blood, which in itself is conducive to chemotaxis of leukocytes.

Experiments were carried out to ascertain what grade of sustained intraenteric tension is necessary to produce anatomic changes in the wall of the bowel. The effects of such distention on its viability and its permeability were simultaneously studied.

Higher levels of increased intraenteric pressure resulted in correspondingly greater degrees of pathologic phenomena. Closed ileal loops subjected to a constant

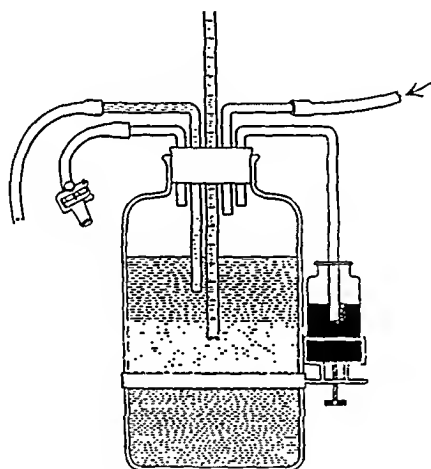


Fig. 6.—Constant pressure bottle of Perusse.

pressure<sup>42</sup> (fig. 6) of 10 cm. of water for twenty-eight hours revealed congestion of the bowel with petechial hemorrhages on the antimesenteric border. There was no marked change in the diameter of the bowel. Viability was not impaired, since active contraction followed stimulation with the faradic current. Permeation of the wall of the bowel by potassium ferrocyanide could not be demonstrated. A loop subjected to a pressure of 15 cm. of water for eighteen hours was much congested; there were hemorrhage into the lumen of the bowel and gangrenous patches on its antimesenteric border. Loops subjected to a pressure of 20 cm. of water for a similar period were dilated to two or three times the normal size and showed congestion of the wall of the entire bowel, with hemorrhagic infarcts on the antimesenteric border, and areas of early necrosis through which penetration of potassium ferrocyanide could be demonstrated. A pressure of

41. Downey, H.: Reaction of Blood and Tissue Cells to Acid Colloidal Dyes Under Experimental Conditions, *Anat. Rec.* **12**:429-448, 1917.

42. Perusse, G. L. Jr.: The Solution of Choice in Proctoclysis, *Surg., Gynec. & Obst.* **54**:770-784, 1932.

40 cm. of water was tolerated for only seventeen hours before gangrene and necrosis ensued. At this pressure the loops were dilated and invariably showed large gangrenous areas with loss of viability and abnormal permeability. Loops of colon subjected to pressures of 30 and 50 cm. of water for twenty-four hours showed similar changes. Loss of viability was encountered only in necrotic areas. Abnormal permeability of the bowel was present through these areas, but never through viable bowel. It is significant that in 1 of these experiments the bowel did not become permeable until six hours after loss of viability was demonstrated (table 11).



Fig. 7.—Dog's ileum subjected to a pressure of 15 cm. of water for eighteen hours. Note hemorrhage into the lumen of the bowel, submucosal hemorrhage and infiltrated and necrotic areas in the muscular layers.

The microscopic observations (figs. 7, 8, 9 and 10) were as follows:

1. Congestion and dilatation of capillaries at a pressure of 10 cm. of water.
2. Extravasation of blood into the tissue spaces and into the lumen of the bowel at a pressure of 15 and 20 cm. of water.
3. Early mononuclear cellular infiltration in the submucosa, even at a pressure of 10 cm. of water.
4. Areas of gangrenous and necrotic tissue in all layers after twenty-four hours of distention at pressures of 20 or 40 cm. of water.

5. Infiltration of all layers of the bowel wall by polymorphonuclear leukocytes, especially concentrated in areas of necrosis.

Repeated tests of the animals' serums gave uniformly negative reactions to injection of prussian blue, indicating that potassium ferrocyanide is not absorbed from the lumen of the bowel even under conditions of increased tension. Positive results from a test of the serosal surface of the bowel indicated passage of the chemical directly through the wall of the bowel. When potassium ferrocyanide was injected

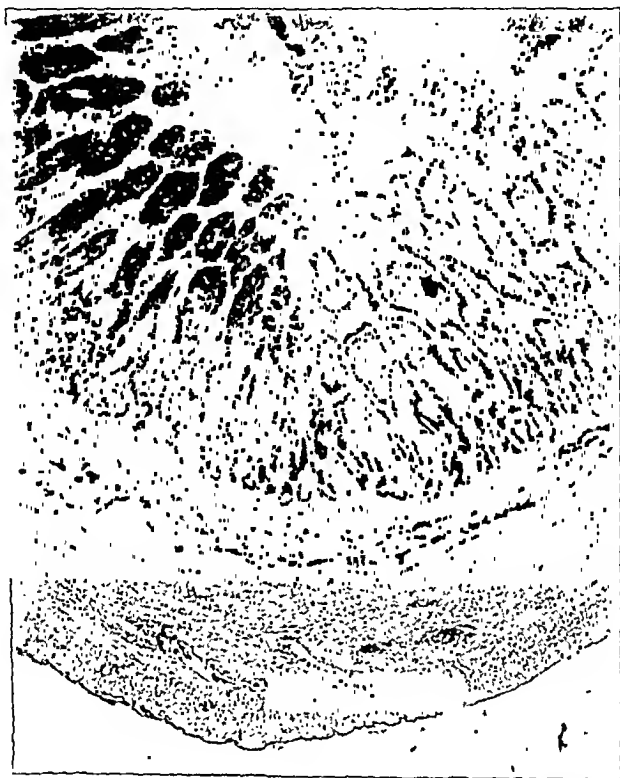


Fig. 8.—Dog's ileum subjected to a pressure of 20 cm. of water for thirty-two hours. Note hemorrhage into the lumen and necrotic areas in the submucosa and in the muscular layers.

intravenously in control experiments, the blood serum fifteen minutes later always gave a positive reaction.

The lesser anatomic effects observed at similar intervals in clinical cases as well as in experimental cases of simple obstruction of the small intestine, as contrasted with the results of a continuously maintained intraenteric pressure as related here, indicate that opportunity must exist in simple intestinal obstruction for occasional release from the pressures observed, which were regarded as sustained. Clinically, in obstruction of the colon (virtually a short closed loop, so made by the competent

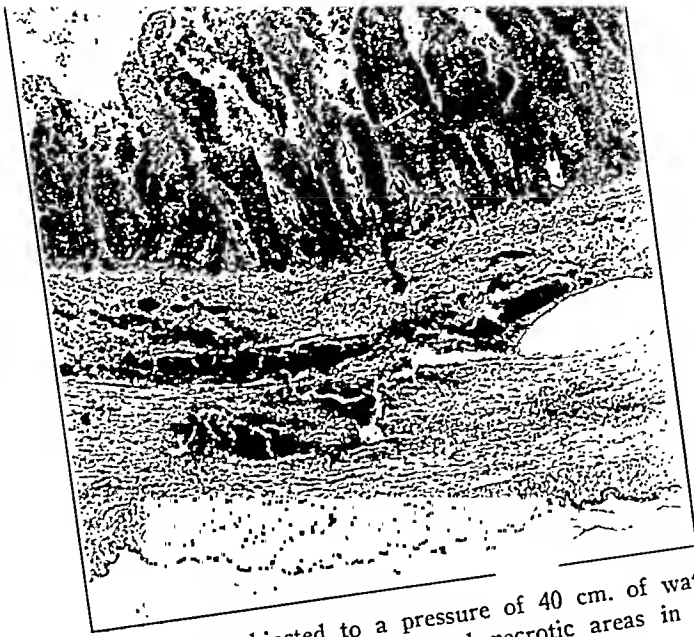


Fig. 9.—Dog's ileum subjected to a pressure of 40 cm. of water for twenty hours. Note hemorrhage into the lumen and necrotic areas in the submucosa and the muscular layers.

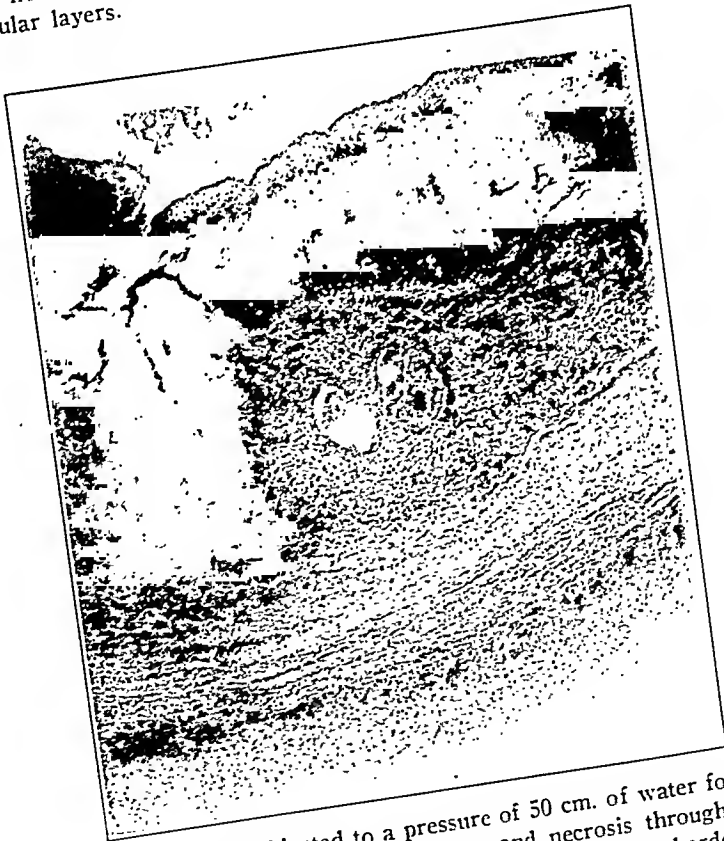


Fig. 10.—Dog's colon subjected to a pressure of 50 cm. of water for twenty-four hours. Note areas of hemorrhagic infiltration and necrosis throughout all layers of the intestinal wall. (Section taken from the antimesenteric border.)

ileocecocolic sphincter) a closer counterpart of the effects of long-maintained intraenteric tension exists. The time necessary for the production of the anatomic and physiologic changes in such obstruction, moreover, is also considerably greater than that observed in these experiments—a fact which denotes that even in closed loop obstruction, in which the intraenteric pressure may be great, the intestine may, by dilating, protect itself to some extent from the effects of distention.

It is concluded from these experiments that:

1. There is a definite relation between the height of intraenteric pressure and the degree of pathologic change occurring after distention of the bowel.

2. Petechial hemorrhage can be demonstrated in the wall of the bowel when a constant pressure of 10 cm. of water is sustained over a sufficient period (twenty-four hours). A pressure of 20 cm. of water sustained for a similar period produces necrosis, loss of viability and abnormal permeability of the wall of the bowel. A sustained intraenteric pressure of 40 cm. of water will produce similar changes in seventeen hours.

3. Abnormal permeability of the intestinal wall does not occur unless its viability is impaired.

#### LETHAL FACTORS IN SIMPLE LOW ILEAL OBSTRUCTION

Any consideration of the factors contributing to the fatal outcome in low ileal obstruction must include all of the following:

1. Loss of fluid and of electrolytes by vomiting and by failure of the distended intestine to absorb a normal amount of fluid.

2. The effect of obstruction on the intestinal wall as it is related to (a) the mode of absorption of any toxic material from the lumen of the bowel, (b) alterations of the normal function of the bowel and, (c) impairment of the integrity of the intestinal wall.

No single factor is responsible for the fatal outcome in all cases, but death is probably due to any of several combinations of these factors.

The part played by dehydration in this type of obstruction varies considerably. When vomiting is profuse, dehydration and the associated alteration of the metabolites of the blood may be severe. However, these changes alone cannot account for the death of the animal, for, as previously indicated, the survival period of animals with low ileal obstruction usually cannot be materially lengthened by the administration of saline solution or Ringer's solution. The factor of loss of fluid assumes serious proportions only in cases of high obstruction of the small intestine. In these cases saline solution affords an effective substitute for the fluid lost.

Although many toxic substances have been isolated from the intestinal contents of animals with ileal obstruction, direct proof of their absorption and of the actual avenue of absorption is lacking. A tremendous amount of literature has accumulated dealing with the possible toxic factor, but as yet concrete evidence to the effect that a specific toxin is absorbed and is responsible for the fatal issue is not available. It is granted that the content of the obstructed bowel is toxic when injected intravenously, but so is the content of the normal bowel. The fact that such material, injected intravenously or by some other parenteral route, produces toxic symptoms does not prove anything more than that, for in carrying out such experiments the normal capacity of the mucosa to protect the organism against fatal infection and other menaces is entirely overlooked. If any toxin is absorbed through the mucosa, it may be by way of the lymphatics, since, as has been shown, absorption by all other normal avenues is decreased when the bowel is obstructed. It is significant that bacteria may be demonstrated in the mesenteric lymph nodes in far greater numbers in the obstructed bowel than in the normal bowel. Nevertheless, ligation of the lymphatic pedicle at the root of the mesentery does not prolong the survival of animals with simple intestinal obstruction.

Transperitoneal absorption must be considered a manifestation of impaired viability of the bowel which has been subjected to distention for a sufficient time to produce gross anatomic changes. Its occurrence is probably insignificant as long as the bowel remains viable, but it may become significant when a devitalized segment is subjected to prolonged distention. The intraenteric pressure, the duration of distention and the diameter of the intestinal coils determine the effect of the distention on the blood supply of the intestine and, in time, the presence or absence of gross anatomic changes and loss of viability of its wall which permit transperitoneal absorption to take place.

That the derangement of normal function which occurs at the level of obstruction is an important factor in the fatal issue is suggested by the following experiment.<sup>43</sup>

Ileosigmoidostomy was performed in 7 dogs in an attempt to alter the function of the terminal portion of the ileum by adapting it to the conditions of the colon as regards (1) stasis, (2) absorption of water and (3) bacterial flora. After periods varying between two and eight and one-half months, simple ileal obstruction was produced at the sites of the anastomoses. Three dogs survived for twenty-five, thirty-one and thirty-four days respectively. This period of survival is considerably longer than that of dogs with simple low ileal obstruction. A loss of 28 to 40 per cent of body weight occurred before death. Death was

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43. Sperlberg, L., and Wangenstein, O. H.: Effect of Previous Ileostomy on the Survival Period of Dogs with Low Ileal Obstruction, *Proc. Soc. Exper. Biol. & Med.* **31**:323-326, 1933.

apparently due to starvation, but it is significant that at autopsy structural changes, which in the light of previous experiments might conceivably permit transperitoneal absorption of a toxin, were evident in the wall of the bowel. These were areas of hemorrhagic necrosis on the antimesenteric border of the bowel, and in one case there was ulceration of the mucosa. Alteration of the chemical constituents of the blood was manifested by a reduced plasma chloride content and by elevation of the nonprotein nitrogen (table 18).

It is conceivable that in these experiments the ileum assumed the function of the colon, that is, the absorption of water, and accommodated itself to the conditions of the colon. Thus those functions which would ordinarily be lost to the dog in a case of low ileal obstruction because

TABLE 18.—Summary: *Ileosigmoidostomy Series*

Dog	Dura- tion of Ileoco- lostomy, Mo.	Survival Period After Obstruc- tion, Days	Saline Given	Weight Loss, %	Blood Chemistry Before Death*		Pathologic Picture
37	2	8	No	17.6	Cl.	412	Distention and rubor of bowel wall
					U.	35.0	
23	2	10	No	17.0	Cl.	305	Abscess about colon closure
					U.	33.0	
					N.P.N.	65.0	
45	3½	12	Yes	14.8	Cl.	264	Volvulus; segment of small bowel with stran- gulation
					U.	18.8	
					N.P.N.	37.2	
79	6	10	Yes	7.0	Cl.	379	Hemorrhagic necrosis on antimesenteric border
					U.	50.0	
					N.P.N.	80.0	
71	3½	25	Yes	23.0	Cl.	346	Hemorrhagic areas of necrosis on antimesen- teric border
					U.	11.5	
					N.P.N.	22.5	
70	8	34	Yes	29.0	Cl.	346	Closed loop formed by adhesions; hemorrhagic necrosis on antimesenteric border; ulceration of mucosa
					N.P.N.	37.0	
74	8½	31	Yes	40.0	Cl.	478	Hemorrhagic necrosis on antimesenteric border
					N.P.N.	20.0	

\* Cl. indicates chlorides; U., urea nitrogen; N.P.N., nonprotein nitrogen.

of the exclusion of the colon (below the obstruction) were preserved. The death of the dogs was then delayed until other factors, such as devitalization of the wall of the intestine due to progressive increase of distention, were sufficiently influential to produce abnormal permeability of its wall and to allow the transperitoneal absorption of some toxin.

#### COMMENT AND SUMMARY

Prior to 1930 a great deal of emphasis was placed on the alteration of the metabolites of the blood in intestinal obstruction, and there was a tendency to relegate the consideration of the local changes in the wall of the bowel to a position of secondary importance. That pathologic changes frequently occur in the wall of the bowel under conditions of obstruction and that they are important factors in the fatal issue has



since been stressed by many investigators. These changes are usually attributed to the impairment of the circulation of blood to the intestine by distention. Most of the recent experimental work has dealt with the effect of distention of the bowel on the intestinal circulation. It has been demonstrated that the flow of blood is decreased as the pressure within the intestine is increased (Dragstedt<sup>24</sup>). Many investigators have referred to the damaging effect of increased intraenteric pressure on the intestinal wall. There has been no previous work establishing the exact level of the intraenteric pressure necessary to produce such changes. In most of the experimental work reported heretofore, extremely high pressures, much higher than those which occur in clinical cases of intestinal obstruction, were utilized (Gatch<sup>28</sup>). From this study it appears that definite pathologic changes can be produced in the wall of the intestine by sustained pressures which are much lower than those used by other investigators and which are comparable to the levels actually measured in experimental and clinical cases of intestinal obstruction.

Observations were made of the effect on the wall of the bowel of sustained and increased intraenteric pressure of the degree measured in experimental and clinical cases of intestinal obstruction. It was determined that diffusion of potassium ferrocyanide, strychnine or dyes through the wall of the intestine into the peritoneal cavity does not occur as long as the intestine remains viable. Although a pressure of 10 cm. of water sustained for twenty-four hours produces petechial hemorrhages in the wall of the intestine, the intestine remains viable and is impermeable to potassium ferrocyanide. Higher pressure (20 cm. of water) is, however, tolerated for only ten to twenty-two hours and results in congestion of the intestine. When this degree of pressure is sustained over a longer period (twenty-four hours) necrosis occurs and permeation of the necrotic areas by the test substances can be demonstrated. Still higher pressures (40 cm. of water or more maintained for eleven hours) result in hemorrhage, necrosis and loss of viability with permeation of the wall of the bowel. However, such pathologic changes are not regularly observed at autopsy after experimental simple ileal obstruction. This emphasizes the importance of the ability of the hollow muscular viscera, such as the bowel and the bladder, to accommodate themselves to alterations of volume without significant changes in the intraenteric tension. Undoubtedly the intestine is able to maintain, within certain limits, an adequate blood supply, despite the compression of the capillaries and of the small venules which follows the increase of intraenteric tension. This may be due to a dilation or stretching of the circular muscle fibers of the intestinal wall. Moreover the dilation of the intestine in experimental and clinical obstruction occurs so gradually that considerable distention may be present without a great increase of tension.

The influence of obstruction on the physical character of the wall of the intestine was investigated. The intestine was found to become shorter by as much as 33 per cent of its initial length, and increased by more than 100 per cent in weight. When allowance has been made for the decrease in length, the actual increase in the weight of the obstructed bowel was found to be 34 per cent. Its water content was found to be increased only 7 per cent, and the amount of blood in the wall of the intestine was increased from one to ten times the normal amount. The tensile strength of the small bowel which has been subjected to simple obstruction was found to be considerably reduced when compared with that of the normal bowel.

The effect of distention on intestinal tone and peristalsis has been discussed. It has been shown that increasing the pressure results in increase of peristalsis, which is most marked in the ileum at pressures between 15 mm. and 30 mm. of mercury. Sudden decompression of the distended intestine provokes violent peristaltic activity. Tone has been demonstrated to be more important than small changes of volume in affecting peristalsis and intraenteric pressure.

It has been well established by previous investigators that, while secretion is increased under conditions of obstruction, absorption is diminished, thus further augmenting the hydraulic factor which operates in a vicious cycle. In this study there was a marked decrease in absorption of all substances tested.

Under identical experimental conditions a closed loop of normal ileum absorbs in one hour approximately 90 per cent of the amount of water necessary to fill it, while a loop of ileum which has been subjected to simple ileal obstruction absorbs less than 10 per cent. The obstructed bowel reacts to increase of tension in exactly the same manner but to a lesser degree than does the normal bowel. The optimal pressure for absorption of water was found to be 40 cm. of water in both groups. There was a significant difference between the amount absorbed by the obstructed intestine and that absorbed by the normal intestine at pressures between 20 cm. and 60 cm. of water (fig. 5).

Lymphatic absorption of dyes and of bacteria is enhanced by the conditions of obstruction and by increased intraenteric pressure. In intestinal obstruction, especially of the closed loop type, dyes and bacteria have been demonstrated in the regional mesenteric lymph nodes. They could not be recovered from the chyle of the thoracic duct. These findings are in accord with those of Costain,<sup>44</sup> Murphy and Brooks,<sup>45</sup>

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44. Costain, W. A.: Lymphaticostomy in Intestinal Obstruction, *Surg., Gynec. & Obst.* **38**:252-255, 1924.

45. Murphy, F. T., and Brooks, B.: Intestinal Obstruction: Experimental Study of the Causes of Symptoms and Death, *Arch. Int. Med.* **15**:392-412 (March) 1915.

and Stone and Firor,<sup>5</sup> who have emphasized the importance of the lymphatics as an avenue for absorption in obstruction. However, severance of the mesenteric lymph pedicle in cats with intestinal obstruction to prevent absorption of toxins through the lymphatics did not lengthen the period of survival. Thus, no evidence was adduced to indicate that the occurrence of increased lymphatic absorption is of much significance in the causation of death of animals with intestinal obstruction.

This work emphasized the significance of the mechanical factors in simple intestinal obstruction. The ill effects of obstruction can all be traced to the effect of distention on the wall of the bowel. The factor of loss of fluid, while important in high intestinal obstruction, has been shown by other investigators to be unrelated to the duration of survival in cases of low ileal obstruction. The main consideration appears to be the viability of the intestinal wall. The normal intestine prevents transperitoneal migration of bacteria and of substances which are toxic when absorbed through the peritoneal cavity. A sustained high intraenteric pressure results in impairment of the viability of the wall of the intestine and thus allows transperitoneal absorption. Relatively low pressures (20 to 40 cm. of water) maintained over a sufficiently long period produce structural changes in the intestinal wall and allow this process to take place.

In view of what has been said in the previous sections on the effect of distention in simple ileal obstruction on the function and the structure of the wall of the intestine, the sequence of events in the development of the changes described may be summarized in the following manner: With the onset of intestinal obstruction there is stasis of fluid and gas within the bowel. The stasis produces a slight increase of intraenteric pressure and a moderate degree of distention, which stimulate the normal bowel to increased peristalsis. Distention and increased intraenteric pressure result in an augmented secretion of intestinal juices, which adds to the content of the bowel. Absorption is decreased early in the course of the obstruction. There is thus a progressive increase of distention and of intraenteric pressure. With a rise in intraenteric pressure there is eventually manifested interference with the circulation of blood to the wall of the intestine. Venous stasis ensues and causes infiltration of the intestinal layers with leukocytes. Eventually hemorrhagic infarction, necrosis and even perforation of the intestine may take place. If the intraenteric pressure is maintained over a sufficiently long time, the viability of the wall of the bowel becomes impaired and its permeation by toxic material may take place through the gangrenous patches. Death is then due to peritonitis or to absorption of toxic material by way of the peritoneum. Relatively low pressures (20 to 40 cm. of water) if

maintained over a sufficiently long period (seventeen to thirty hours) to produce structural changes in the intestinal wall will allow this to take place.

The processes occurring in simple low ileal obstruction and in closed loop obstruction are listed here:

- Obstruction
- Intestinal stasis
- Distention
- Increased activity of the bowel
- Increased intraenteric pressure
- Increased secretion of intestinal juices
- Decreased absorption
- Further distention
- Violent peristalsis
- Circulatory stasis
- Increased venous pressure
- Anoxemia of the wall of the bowel
- Hemorrhage
- Impairment of viability
- Leukocytic infiltration
- Necrosis and gangrene
- Loss of viability
- Permeability of the wall of the bowel to toxins and bacteria
- Peritonitis

# INTESTINAL OBSTRUCTION

## EXPERIMENTAL EVIDENCE ON THE LOSS OF BLOOD IN INTESTINAL STRANGULATION

HORACE G. SCOTT, M.D.

MINNEAPOLIS

In the past, numerous attempts have been made to ascribe the disastrous effects of all types of intestinal obstruction to some one etiologic factor. Of the many explanations offered, that of intestinal toxemia has been given greatest consideration. Literally hundreds of investigators have tried to show that this or that toxin was the one responsible for the dire results. However, there has been no general agreement as to what toxin was to blame. This, together with the fact that no theory of intestinal toxemia has ever offered any benefit to the patient in the way of improved methods of treatment or lowered mortality, has cast grave doubt on this explanation. The work of the past thirty years, however, has shown that, from an anatomic and pathologic standpoint at least, intestinal obstructions can be divided into two major types or a combination of the two. The terms simple and strangulation obstruction have been used to designate and differentiate the two major forms by clinicians and investigators alike.

The first term, simple obstruction, implies an occlusion of the lumen of the bowel without gross interference with the mural blood supply, while the second, strangulation obstruction, implies a vascular impairment of the wall of the bowel and its mesentery. At operation or necropsy, patients for whom the diagnosis was made clinically not infrequently show some evidence of both types of obstruction. In fact, most strangulation obstructions are accompanied by a simple mechanical or neurogenic obstruction. The reverse is not usually the case. Occasionally, however, a simple obstruction may produce some intramural vascular changes, even to the point of necrosis and perforation of the intestinal wall. This is especially true when a so-called gas trap develops and produces stasis of blood within the wall of the bowel as a result of a pathologically high intrainestinal pressure. This occurs more frequently in the colon, where a neoplastic lesion of the sigmoid

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Abridgment of a thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery.

flexure may produce a closed loop. The usual competency of the ileocecal valve, which prevents the backward passage of gas into the small intestine, may convert such a loop into a gas trap.

Because of a rather frequent combination of simple and strangulating mechanisms, with their overlapping symptom complexes, many patients observed clinically fail to present typical symptoms of either type of obstruction. Therefore, it has been rather difficult for the surgeon and the clinician to realize that two entirely different physiopathologic processes might be responsible for producing the many complex effects of intestinal obstruction. As a result, the symptoms have been erroneously attributed to some one etiologic factor. It is no wonder that the theory of intestinal toxemia has become so firmly rooted in the consciousness of medical practitioners that the concepts advanced in recent years have been but slowly and hesitatingly accepted.

Recently several writers (Wilkie,<sup>1</sup> Murphy,<sup>2</sup> Elman,<sup>3</sup> Scott,<sup>4</sup> Blalock<sup>5</sup> and Mensing<sup>6</sup>) have called attention to the fact that the loss of blood in intestinal strangulations may be of some consequence in bringing about and aggravating symptoms of shock and in causing death. D. P. D. Wilkie,<sup>1</sup> writing in 1913, distinguished clearly between simple and strangulation obstruction. He was impressed with the amount of blood lost in strangulation obstruction and felt that it played an important role in the causation of shock and death. During the course of some experiments on strangulation obstruction in the dog, I also observed significant loss of blood into the walls and lumen of the strangulated bowel. Further experiments were devised to determine the extent of this loss of blood and its relation to changes in blood pressure, shock and death as seen in these conditions. The presentation of the results of these experiments constitutes the main object of this paper.

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1. Wilkie, D. P. D.: Experimental Observations on the Cause of Death in High Obstruction, *Brit. M. J.* **2**:1064, 1913.

2. Murphy, F. T., and Vincent, B.: An Experimental Study on the Cause of Death in Intestinal Obstruction, *Boston M. & S. J.* **165**:684, 1911.

3. Elman, R., and Cole, W. H.: Loss of Blood as a Factor in Death from Acute Portal Obstruction, *Proc. Soc. Exper. Biol. & Med.* **29**:1122, 1932.

4. Scott, H. G., and Wangenstein, O. H.: Blood Losses in Experimental Intestinal Strangulations and Their Relationship to Degree of Shock and Death, *Proc. Soc. Exper. Biol. & Med.* **29**:749, 1932.

5. Blalock, A.: Trauma to the Intestines: The Importance of the Local Loss of Fluid in the Production of Low Blood Pressure, *Arch. Surg.* **22**:314 (Feb.) 1931.

6. Mensing, E. H.: Intestinal Obstruction: Application of Newer Principles Evolved from Experimental and Clinical Experience, *Am. J. Surg.* **17**:206, 1932.

## METHOD OF EXPERIMENTS

In order to evaluate the role that the arteries and veins may play individually and collectively in determining the period of survival of dogs with strangulation obstruction, the experiments here reported were divided into four groups according to the type of strangulation produced. Variations in the length of intestine obstructed also were taken into account. In the creation of the various types of obstruction described in this paper,  $\frac{1}{4}$  to  $\frac{1}{2}$  grain (16 to 32 mg.) of morphine sulfate and  $\frac{1}{150}$  to  $\frac{1}{75}$  grain (0.4 to 0.9 mg.) of atropine sulfate were given preoperatively to each animal. Ether was used as the anesthetic in every instance, and sterile technic was employed throughout.

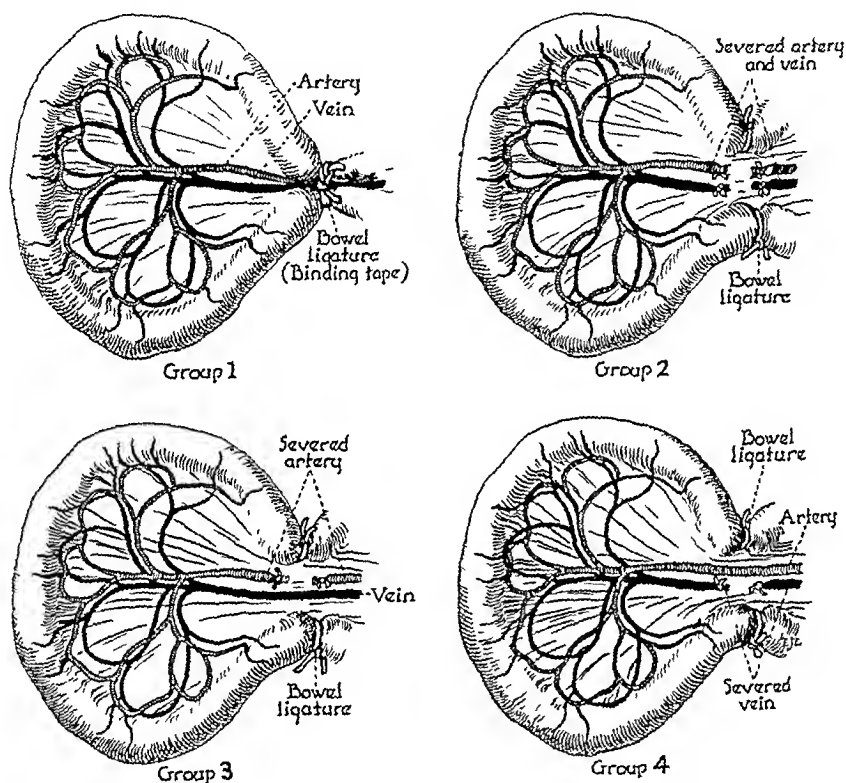


Fig. 1.—The four methods employed in producing the experimental strangulation obstructions recorded in this paper. Group 1 presents a partial occlusion of lumen and blood supply; group 2, a complete occlusion of blood supply; group 3, a complete arterial occlusion with patent vein, and group 4, a complete venous occlusion with artery intact.

*Type of Obstruction.*—In group 1 no attempt was made to control the relative degree of arterial or venous occlusion of the strangulated intestinal loops. In this way it was hoped that some idea might be obtained of the variations in length of life which one might encounter experimentally when a constricting band was passed about the mesenteric pedicle and the wall of the bowel. Binding tape, 1 cm. in width, was passed about the mesenteric vessels and then carried around the wall of the bowel and tied. The lumen of the bowel as well as its blood supply was thus occluded. The method is illustrated in figure 1. An experimental volvulus,

or adhesive band type of strangulation, was thus brought about, which simulated closely the variations in this type of obstruction usually met in clinical experience.

In groups 2, 3 and 4, binding tape was used merely to occlude the lumen of the bowel at the ends of the segment strangulated. A window was first made in the mesentery adjacent to the wall of the bowel at the ends of the loop selected. The anastomosing vessels adjacent and parallel to the wall of the bowel were cut and ligated. The binding tape was passed about the wall of the bowel and tied. The mesenteric vessels were then occluded by ligating and severing them individually or collectively, according to the type of obstruction desired. In group 2, all the arteries and veins to the loop selected were ligated and severed. In group 3, all the arteries were ligated, but the veins were left intact. In group 4, all the veins were ligated but the arteries were left intact. Figure 1 illustrates the four different types of obstruction produced. After operation the animals were returned to their cages or kept on the operating table while their blood pressure was being recorded on the kymograph. No particular postoperative treatment was given. Most of the experiments being of an acute nature, problems of feeding and hydration did not have to be considered. Immediately after death the animals were subjected to careful autopsy.

## RESULTS

*Pathologic Observations at Autopsy.*—At autopsy a marked difference was noted in the appearance of the strangulated bowels in the various groups. In group 1 (obstruction by encirclement), the peritoneal cavity was found to contain from 30 to 140 cc. of bloody serous fluid. The hemoglobin content of this fluid was found to vary between 3 and 10 per cent. The bowel itself was always moderately distended. The color was usually a deep purple or dark mahogany. The degree of distention apparently varied with the degree of tension on the mesenteric pedicle. The greater the tension the less the distention, apparently because the arterial blood was prevented from entering the wall and lumen of the bowel. The serosa in most cases was found to have a fibrinous exudate over its surface, although in some few instances little or no fibrin was present. When the bowel was sectioned, the wall was seen to be definitely thickened. The lumen was observed to contain a moderate amount of dark bloody fluid or actual blood clots. The hemoglobin content of this fluid was found to vary between 60 and 140 per cent. On microscopic as well as gross section, the wall of the bowel was observed to be markedly thickened in comparison with its normal condition. The reason for this increase was apparent on examination. The mucosa, especially, was seen to be packed with red blood cells. There were hemorrhages into the muscular layers as well.

In group 2 (complete arteriovenous obstruction), the peritoneal cavity was found to contain 40 to 350 cc. of a dark, foul-smelling bloody fluid when the strangulated loops showed gross rupture. When the loops remained intact the peritoneal cavity contained less fluid, which was less hemorrhagic and not nearly so foul smelling. The hemoglobin



content of this fluid was usually less than 10 per cent. Examination of the bowel revealed it to be lusterless, dark purple or mahogany colored and moderately distended with bloody fluid when not ruptured. In this group and in the next (arterial obstruction), in which the pathologic findings were practically identical, 18 of 28 animals had loops which were ruptured in one or more places at the time of death. The wall of the intestine in these animals was usually thinner than normal, extremely friable and jelly-like. There were a few exceptions to these general statements. On 3 or 4 occasions, the intestine was found to be a patchy grayish yellow green; the wall was not perforated and the lumen not distended. This type of infarction was termed anemic

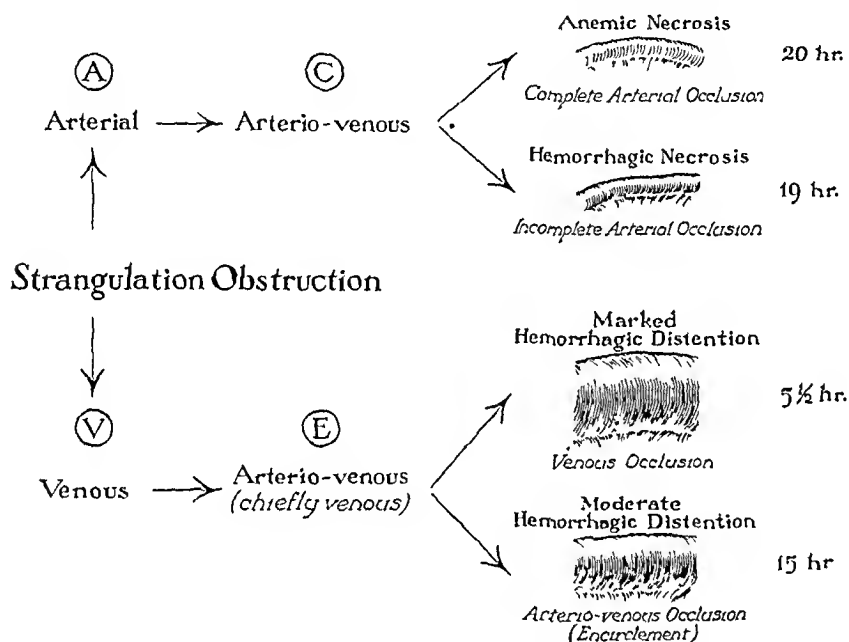


Fig. 2.—The various types of strangulation obstruction that may result, according to the relative degree of venous or arterial occlusion. When the arterial obstruction predominates there is little or no distention, whereas when the venous obstruction predominates there is a moderate to marked distention with blood.

necrosis, in contrast to the usual hemorrhagic necrosis seen in other types of strangulation. A careful analysis of the methods employed revealed the cause for the hemorrhagic necrosis in some instances and the anemic necrosis in others. In the cases of hemorrhagic necrosis blood apparently gained access to the wall of the bowel through the capillary bed of the mesentery proper, whereas no blood at all entered the bowel in the cases of anemic necrosis.

In group 3 (arterial obstruction), the pathologic picture, as previously stated, was practically the same as in group 2. In group 4, the

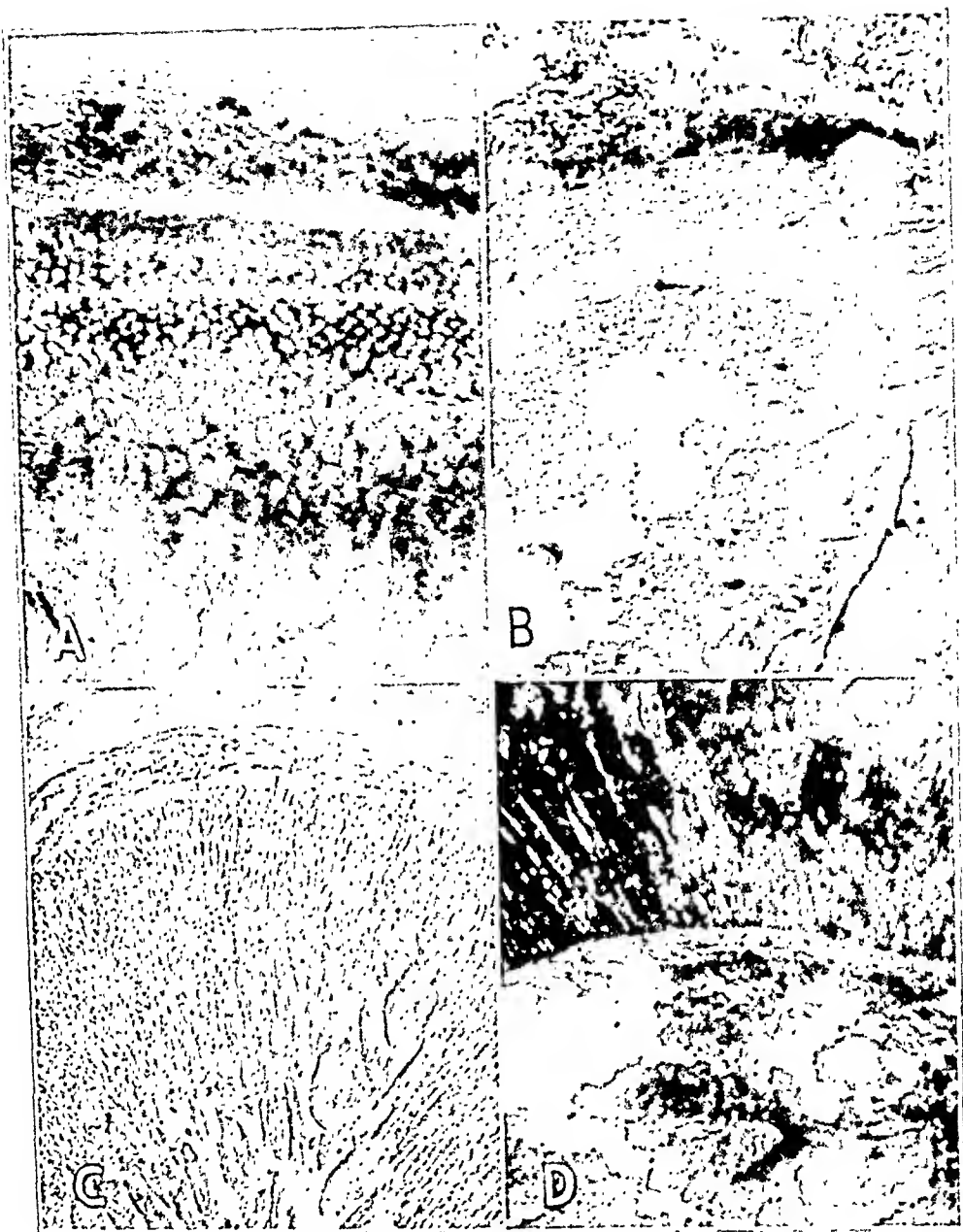


Fig. 3.—*A*, photomicrograph of an ileum after an encirclement ligature had been tied about the wall of the bowel and the mesentery for two hours. Note the thickening of the mucosa and submucosa, the villi being packed with blood cells. Note the blood in the submucosa and the hemorrhages in the muscular layers. *B*, photomicrograph of an ileum in which the arteries and veins had been completely severed for fifteen hours. This is grossly a case of hemorrhagic necrosis. Note the sloughing mucosa and serosa and the absence of any definite muscular layers. *C*, photomicrograph of an ileum in which the arteries and veins had been completely severed for thirty hours. Note the essentially normal histologic picture, except for the general atrophy of all layers of cells and the slight amount of blood in the tips of the villi. *D*, photomicrograph of an ileum in which the veins had been completely ligated for four hours. Note the massive hemorrhages into all layers. This is grossly a case of marked hemorrhagic distention. Note how the muscle bundles are torn apart. Only the serosa and the basement layer of mucosa remain intact in this section.

pathologic changes were almost identical with those in group 1, except that they were all more marked. The peritoneal fluid was present in larger amounts, the quantity ranging between 30 and 300 cc. The degree of distention of the bowel was likewise more marked. When the bowel was opened it was seen to contain rather large amounts of bloody fluid with a hemoglobin content ranging between 90 and 140 per cent (Sahli).

*Increase in Weight of Strangulated Loops of Intestine.*—When the strangulated bowels in groups 1 and 4 were weighed after the conclusion of the experiments, they were noted to have increased in weight over estimates based on a series of normal weights. The increase was from 133 to 235 per cent in group 1 and from 150 to 490 per cent in group 4. This increase was due solely to blood cells and plasma which had accu-

TABLE 1.—*Percentage of Increase in Weight of Strangulated Loops of Ileum in Eighteen Dogs*

	Weight of Dog, Kg.	Length of Intestine, Ft.	Weight of Intestine, Gm.	Normal Weight, Gm.	Percentage of Increase in Weight
<b>Group 1 (encirclement of pedicle)</b>					
Minimum.....	11	2.0	240	76	133
Maximum.....	21	5.0	675	150	320
Average.....	15	3.2	460	103	235
<b>Group 4 (ligation of veins)</b>					
Minimum.....	8	3.0	260	90	150
Maximum.....	22	5.5	1,080	170	490
Average.....	15	4.3	680	135	235

mulated within the lumen and the wall of the intestine during the period of strangulation. Table 1 gives the minimum, maximum and average weights of strangulated bowels obtained at autopsy from a series of 18 dogs, 7 being in group 4 and 11 in group 1. The figures for normal weights of intestines are estimates based on tabulations of weights of given lengths of small intestine taken from 10 normal dogs. The average weight for 1 foot (30 cm.) of normal ileum was found to be approximately 30 Gm. and 1 foot (30 cm.) of normal jejunum 35 Gm. Table 1 shows in percentage the increase in weights of strangulated loops of ileum in 18 dogs.

*Total Protein Content of Peritoneal Fluid.*—From the gross pathologic condition of the bowels, the microscopic picture and the increase in weight of the intestine, it was evident that a rather large amount of blood was lost into the lumen and the wall of the bowel. This was especially true in the group with patent arteries and ligated veins. The peritoneal cavity, as already noted, was observed to contain a moderately large amount of clear blood-tinged fluid. Calculations of total protein content of the peritoneal fluid were made in three of the groups,

those in which venous, complete and arterial ligation, respectively, were performed. The group in which the pedicle was encircled was omitted, because it was felt that any differences which might be found in this group would lie well within the extremes of the group with venous ligation, on the one hand, and that with arterial or complete ligation, on the other. Table 2 gives the data in 17 experiments in which the total protein content of the peritoneal fluid and blood plasma was determined at operation or at the time of the animal's death. The total protein content of the blood plasma was determined on samples of blood drawn at the time of the removal of the peritoneal fluid. It will be noted that when the loop of bowel was not ruptured the total protein content of the peritoneal fluid was practically the same as that of the animal's own blood plasma. When the loop was ruptured, the protein content rose to as high as twice that of the blood plasma. It will be

TABLE 2.—*Total Protein Content of Peritoneal Fluid in Twenty-One Dogs with Strangulated Loops of Ileum*

	No. of Dogs	Type of Obstruction	Average Length of Strangulated Bowel, Ft.	Average Time of Strangulation, Hr.	Average Total Protein Content of Blood	Average Total Protein Content of Peritoneal Fluid
Group 2	10	Arterial and venous	2.2	26.6	5.38	6.47
Group 3	6	Arterial	3.0	11.3	5.62	6.32
Group 4	5	Venous	3.8	4.1	5.10	4.69

seen that in the group with venous ligation, at least, the peritoneal fluid is not unlike the animal's own blood plasma, having a practically equivalent total protein content.

*Effect of Intravenous Injections of Peritoneal Fluid.*—In order to determine whether or not the peritoneal fluid of animals suffering from the various types of strangulation obstruction was toxic, portions of it were collected at operation or autopsy and introduced into the veins of the legs of normal dogs. The amounts varied between 20 and 185 cc. No attempt was made to filter, heat or treat this fluid in any way. It was collected under aseptic technic and introduced with a sterile needle and syringe. At the time the fluid was introduced into the vein of the leg a tracing of carotid blood pressure was made with the animal under light ether anesthesia. Fifteen experiments were carried out on 14 different dogs. There were no immediate or delayed effects in 10 of the animals. These 10 animals had been given peritoneal fluid obtained from animals that died without gross rupture of the strangulated loops. In the 4 remaining animals there was an immediate effect which consisted of a marked sudden fall in blood pressure followed by a sharp rise. By the next day all 4 animals had died of generalized gas bacillus

infection. Three of these 4 had received peritoneal fluid obtained from animals in which the loop had ruptured prior to death. The fourth animal from which peritoneal fluid had been taken died with an intact loop, but the wall of the intestine was necrotic. The peritoneal fluid obtained from this animal, as well as that from the 3 with ruptured loops, had a foul odor, and bacteriologic studies revealed the presence of innumerable bacteria, both anaerobic and aerobic.

In the 10 animals that showed no immediate effect other than a slight rise in blood pressure there was likewise no delayed effect. Within an hour or two after the discontinuance of the anesthesia, the animals

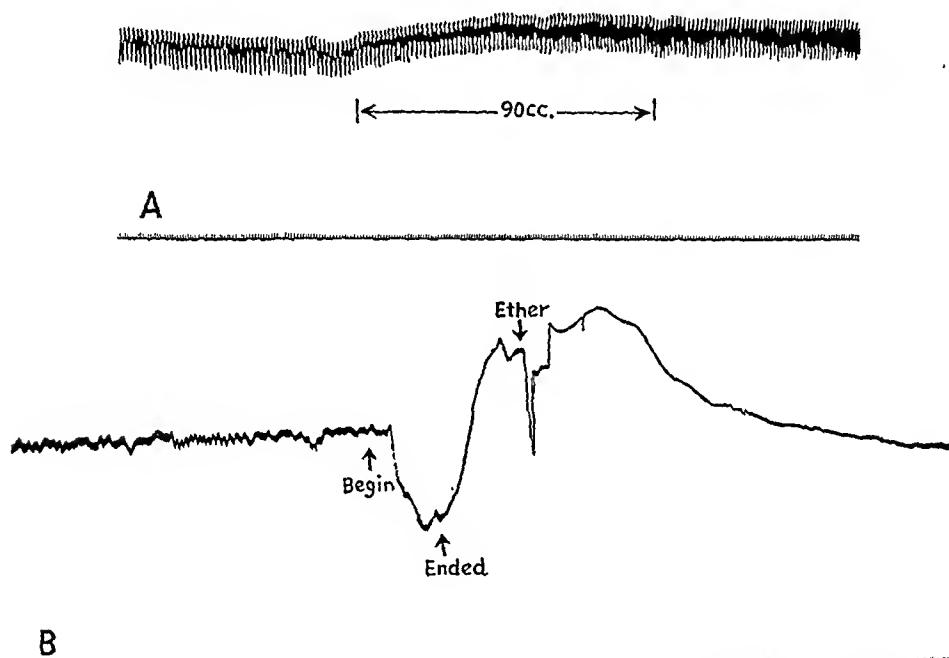


Fig. 4.—*A*, effect on the carotid blood pressure of a normal dog of injecting intravenously 90 cc. of peritoneal fluid from a dog with a strangulation obstruction (encirclement) of eighteen hours' duration. The strangulated loop of bowel was not grossly ruptured. The recipient suffered no immediate or delayed effect. *B*, effect on the carotid blood pressure of a normal dog of injecting intravenously 40 cc. of peritoneal fluid from a dog with a strangulation obstruction (ligation of arteries and veins) of fifteen hours' duration. The strangulated loop was grossly ruptured. The recipient died by the following morning.

were up and about as usual. The next day they ate well and appeared normal in all respects. The tracings shown in figure 4 are typical of the effects which have been described. From these experiments it may be concluded that the peritoneal fluid when injected intravenously has no appreciable effect on the blood pressure or general health of the

animal unless the strangulated loop is ruptured or is about to rupture. When death occurs it is apparently due to the intravenous injection of bacteria.

*Absorption of Strychnine Sulfate From the Normal Bowel and From the Strangulated Bowel.*—In view of the controversy concerning the absorption of so-called toxic products from the obstructed bowel, it was deemed wise to test the absorptive power of the normal and of

TABLE 3.—*Effect of Intravenous Injection into Normal Dogs of Peritoneal Fluid from Dogs With Strangulation Obstruction*

Experiment	Duration of Strangulation, Hr.	Condition of Strangulated Bowel	Amount of Injection, Cc.	Effect of Injection on Normal Dogs
33 E*	4	Intact	100	No immediate or delayed reaction in 2 dogs
34 E	5½	Intact	50	No immediate or delayed reaction
36 E	6	Intact	50+ 90 blood serum	No immediate or delayed reaction other than slight (10 mm.) rise and fall in blood pressure
41 E	5½	Intact	185	No immediate or delayed reaction other than slight rise in blood pressure
37 E	6½	Intact	80 + 45	No immediate or delayed reaction other than slight rise in blood pressure
42 E	19	Intact	120	No immediate or delayed reaction other than slight rise in blood pressure
43 E	18	Intact	90	No immediate or delayed reaction other than slight rise in blood pressure
44 E	17	Ruptured	100	Abrupt fall in blood pressure followed by rise, death within 24 hr.
50 V	1	Intact	20	No effect
47 C	7	Intact	20	No effect
45 C	18	Intact, necrotic	20	Abrupt fall in blood pressure to 60 mm., followed by abrupt rise to 135 mm., death within 24 hr.
48 C	15	Ruptured	40	Very abrupt fall in blood pressure to 85 mm., followed by a rapid rise to 240 mm., death within 24 hr.
46 C	27	Ruptured	20	Marked fall in blood pressure followed by gradual rise, death within 24 hr.

\* E, encirclement of pedicle; V, ligation of veins; C, ligation of veins and arteries.

the strangulated intestine for products of known toxicity. Strychnine sulfate was chosen for this purpose, as it produces unmistakable clinical symptoms when absorbed in small quantities. A 50 mg. dose of strychnine sulfate was introduced into the lumen of the normal small intestine in 3 dogs. A similar dose was placed free in the peritoneal cavity in 2 other dogs. All 5 animals showed definite signs of irritability, followed by convulsions in from three to five minutes, and subsequently died. Fifty to 150 mg. of strychnine sulfate was then introduced into the lumens of strangulated loops of bowel immediately after strangulation. The usual four types of strangulation were employed.

In group 1 (by strangulation encirclement), 3 experiments were carried out. One hundred and fifty milligram doses were employed. In all 3 animals convulsions were delayed. In the first animal convulsions developed in about four hours, and death ensued in four and one-half hours. The second and third animals died in convulsions after seven and fifteen hours respectively. The first signs of irritability or convulsions appeared just a few hours prior to death. These results indicate a great delay in absorption as compared with the normal rate. The wide variation in time of development of symptoms was to be expected in this group in view of the fact that no attempt was made to arrest the flow of blood completely, the degree of occlusion depending entirely on the tightness of the encircling tape. The peritoneal fluid was tested for the presence of strychnine after the death of the animal by the injection of 2 to 5 cc. samples of it into the dorsal lymph sacs of frogs, which were then observed for tetanic convulsions. None of the frogs gave a positive reaction, except that in which the sample obtained from the animal that died after fifteen hours had been injected. This animal had a grossly perforated loop, and it was to be expected that its peritoneal fluid would contain strychnine.

In group 2 (complete strangulation), 10 experiments were carried out. Six animals showed no sign of convulsions, while delayed convulsions developed in 4. Death occurred in these animals after six, seven, twelve and fourteen hours respectively, and convulsions were first observed in each instance only an hour or two before death. When the peritoneal fluid from these 4 animals was tested by injection into frogs, the presence of strychnine was indicated only in the postmortem specimen from the animal that died after twelve hours. Of the 6 animals that died without tetany or convulsions, the same test indicated the presence of strychnine in the postmortem specimen from only 1, which had lived thirty hours after strangulation. The strangulated loop in this animal was extremely necrotic and friable but not grossly perforated. In group 3 (arterial obstruction), 10 experiments were carried out. None of the 10 animals showed signs of strychnine poisoning. There was some evidence of minute amounts of strychnine in the peritoneal fluid, as convulsions developed in from twelve to forty-five minutes in 3 frogs into which it was injected. In group 4 (venous obstruction), 9 experiments were carried out. Convulsions developed in 3 of the 9 animals. The explanation for these results was evident at autopsy, when the normal adjacent intestine was seen on being opened to contain bloody fluid from the strangulated loop.

Although these experiments might seem to indicate that toxic products can be absorbed from the strangulated bowel, one must remember that when convulsions did occur they were greatly delayed. Moreover, as pointed out in reference to the last group, the possible avenue of

absorption from the adjacent normal bowel must not be overlooked. While strychnine is readily absorbed from the normal bowel, as the control experiments showed, numerous workers have failed to find any evidence of absorption of "toxins" contained in strangulated loops from normal bowel. However, there is no denying that traces of strychnine probably pass through the wall of the bowel the nutrition of which has been seriously impaired, since in a number of cases its presence in the peritoneal fluid was indicated by the reactions of frogs into which the fluid was injected.

*Absorption of Histamine and Tetanus Toxin from the Strangulated Bowel.*—It has been noted occasionally that after the release of a strangulating mechanism a patient previously in good condition immediately goes into a state of shock. This fact has been used as an argument for the absorption of a toxic, histamine-like substance. Blalock,<sup>5</sup> however, has recently shown that under such circumstances blood and plasma are lost through the traumatized vessels into the tissue spaces, where they are removed from the general circulation, and a deficit in the volume of blood returning is thus caused. Wangensteen and Loucks<sup>7</sup> could not confirm the absorption of histamine, even though they introduced it into the lumens of strangulated loops. On releasing the strangulating mechanism, they noted not infrequently a fall in blood pressure and sometimes even death. However, they never noted the characteristic drop in blood pressure that one would expect to accompany the absorption of histamine.

These experiments were repeated, with relatively large amounts of histamine, and the authors' results were confirmed. No effect of histamine was noted in any of the tracings of blood pressure which were made. In fact, in 4 animals subjected to a four hour strangulation by encirclement, release of the strangulating ligature after the introduction of 75 to 150 mg. doses of histamine into the strangulated loops caused only a slight gradual decline in the carotid blood pressure in a single instance. Fifty milligrams of tetanus toxin likewise was introduced into the lumen of a completely devascularized loop of bowel in 1 instance. Samples of peritoneal fluid were obtained by aspiration through an intraperitoneal catheter at two hour intervals. These samples (3 to 5 cc.) were injected subcutaneously into white mice. Six mice received injections over a period of twelve hours. They were observed for forty-eight hours, and none showed evidence of tetanic seizures. These experiments indicate that histamine or a histamine-like substance is not absorbed from a previously strangulated bowel. In fact,

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7. Wangensteen, O. H., and Loucks, M.: Studies in Intestinal Obstruction: II. The Absorption of Histamine from the Obstructed Bowel, Arch. Surg. **16**: 1089 (May) 1928.



all the evidence in this and the preceding section would point to a delay rather than an acceleration in absorption from the damaged wall of the bowel. Furthermore, the devitalized wall of the bowel is apparently impermeable to tetanus toxin, at least over a twelve hour period.

*Intraperitoneal Autolysis of Autoclaved Intestine and Intestine Treated with Chemical Antiseptics.*—In order to determine whether the wall of the bowel itself is "toxic," an attempt was made to free the normal intestine of the dog from its usual bacterial flora by chemical and thermal sterilization. Segments of bowel thus treated were placed in the peritoneal cavities of normal dogs, in order to determine their relative and actual degree of "toxicity," as judged from a clinicoexperimental standpoint. In every instance in which segments of intestine were treated with chemical antiseptics for periods varying from five to ten minutes, cultures of mucosal scrapings were observed to contain a great variety of organisms. When these chemically treated loops were

TABLE 4.—*Resulting Mortality in Twenty-Eight Dogs When Segments of Small Intestine Obtained from Other Dogs Were Treated in Various Ways and Introduced into the Peritoneal Cavity*

Number of Experiments	Method	Percentage of Mortality
2	Open loops of ileum, devascularized	100
3	Open loops of jejunum, devascularized	100
2	Devascularized Thiry Vella loops	100
4	Segments of bowel treated with tincture of iodine	100
4	Segments of bowel treated with mercurchrome and alcohol	75
3	Segments of bowel treated with water and ether	100
10	Segments of bowel autoclaved 30 to 45 minutes	10

placed in the peritoneal cavities of 18 normal animals, only 1 survived. In contrast to this, 9 of 10 animals survived that had loops of bowel sterilized by steam placed in their peritoneal cavities. Cultures of the mucosa from the autoclaved loops were negative in all instances. A few organisms must have been present in the mucosa of the bowel in 1 case or have gained entrance at the time of operation, as the animal died five days later of bacterial peritonitis. These results were to be expected in view of the fact that the devitalized intestine and the peritoneal cavity provide bacteria with an ideal culture medium under optimum temperatures. This work substantiates the experimental results of Dragstedt<sup>8</sup> and his co-workers, who showed that it was extremely difficult to sterilize the normal bowel with the usual antiseptics. It also confirms their conclusion that devitalized sterile loops of bowel are harmless.

8. Dragstedt, L. R.; Dragstedt, C. A.; McClintock, J. T., and Chase, C. D. Intestinal Obstruction. II. A Study of the Factors Involved in Production and Absorption of Toxic Materials from the Intestine, *J. Exper. Med.* **30**:109, 1919.  
 Dragstedt, L. R.; Moorehead, J. J., and Burcky, F. W. Intestinal Obstruction. I. An Experimental Study of the Intoxication in Closed Intestinal Loops, *ibid.* **25**:421, 1917.

*Bacteriologic Observations of the Peritoneal Fluid After Strangulation Obstruction.*—Thirty-five centimeter loops of the lower part of the ileum were strangulated for periods varying from two and three-quarters to four and one-half hours with an encircling ligature. Bacteriologic studies were then conducted as follows: As strict aseptic technic as possible was employed at the time of strangulating and taking of cultures. In each study smears were made of the peritoneal fluid, the wall of the bowel and the mesentery. Cultures were made on lactose, liver peptone and brain mediums. Smears were also made of cultures twenty-four and forty-eight hours later. The following organisms were found:

- |                                     |                                      |
|-------------------------------------|--------------------------------------|
| 1. Gram-positive spore-forming rods | 6. <i>Bacillus coli</i>              |
| 2. Gram-positive micrococci         | 7. <i>Aerobacter aerogenes</i>       |
| 3. Gram-positive diplococci         | 8. <i>Streptococcus haemolyticus</i> |
| 4. Gram-negative rods               | 9. <i>Sarcina</i>                    |
| 5. <i>Clostridium welchii</i>       | 10. <i>Staphylococci</i>             |

In 10 experiments there were 6 positive and 4 negative cultures. There were likewise 4 deaths. Three of the deaths occurred within two hours of release and were undoubtedly due to hemorrhage, as will be shown in the succeeding sections. One of these deaths was that of an animal which had entirely negative cultures. Three of those that recovered (50 per cent) had positive cultures. Therefore, the presence of organisms was not as serious a factor in the causation of death as it might seem on the face of it. This fact is mentioned in order to show how much the bacteriologic aspects of intestinal obstruction have been over-emphasized.

*Fall in Hemoglobin Content After Venous Obstruction.*—A definite fall in hemoglobin content was noted in all animals with venous obstruction. The results obtained in 1 animal that died and 2 in which resection of the bowel was carried out are shown in table 5.

*Correlation Between the Fall in Blood Pressure and the Time, Length and Type of Intestinal Strangulation.*—The carotid artery was cannulated in 30 dogs and a tracing made of the blood pressure during the course of vascular occlusions of various types. In each experiment the time as well as the length and site of strangulation of the bowel was noted. In order to control the degree of arterial and venous occlusion, the experiments were divided into four groups, as defined in the preceding sections. In group 1 (obstruction by encirclement), the length of bowel strangulated varied between 1 and 11½ feet (30 to 350 cm.). The time varied between three and seven hours. The blood pressure prior to strangulation was recorded in 5 of these experiments, while the resulting pressure after from three to seven hours was ascertained in every case. The lowest pressure recorded after this interval was 77 mm.

of mercury and the highest 140 mm. In 7 dogs, in which the length of intestine was less than 3 feet (90 cm.), the blood pressure had not fallen in any case below 100 mm. In the 9 remaining dogs, in which the segment strangulated was more than 3 feet (90 cm.) in length, the pressure at the time of release was less than 100 mm. in 6 instances. The time at which the release was effected varied within each division of this group, but the interval was approximately the same in both divisions, with but 1 exception. In group 2, in which the arteries and veins were ligated, the pressure was found to be within normal limits after from four to six hours' observation. Also in group 3, in which the arteries were ligated, the pressure was found to be within normal limits after from four to six hours. Tracings were taken after eighteen and one-half hours in the case of 2 animals which appeared moribund at that time. One showed a mean pressure of 20 mm. and the other of

TABLE 5.—*Decline in Hemoglobin Content of the Blood of Three Dogs in Which Strangulation Obstruction of the Small Bowel with Ligation of the Veins Was Produced*

Dog 303		Dog 304		Dog 305	
Time	Percentage of Hemoglobin	Time	Percentage of Hemoglobin	Time	Percentage of Hemoglobin
8:30 a.m.	103	8:15 a.m.	106	10:00 a.m.	95
9:10	Strangulation	9:50	Strangulation	10:30	Strangulation
9:40		10:20		11:00	
10:40	105	11:20	102	12:00 noon	70
11:40	102	12:20 p.m.	78	12:50 p.m.	68
12:50 p.m.	90	1:20	65	1:50	67
1:50	82	2:10	Resection	1:40	Resection
2:50	76	2:20		2:50	
3:35	Dog dead	3:25	70	3:50	63

70 mm. The first died half an hour later and the second one and one-half hours later; these observations signify that, though it was delayed, there was a definite fall in blood pressure terminally. In group 4, consisting of 10 dogs in which the veins were ligated, the pressure was below 70 mm. in every instance after from one to five hours. Three of the 10 animals were dead within this time. One animal, in which the superior mesenteric vein was ligated, died within one hour. Two of 3 dogs in which the veins to a  $5\frac{1}{2}$  foot (170 cm.) segment were ligated died within four hours, with consistent decline in blood pressure during the course of the experiments. One animal in which the veins to a 5 foot (150 cm.) segment were occluded was still alive at the end of four hours but had a blood pressure of only 54 mm. The remaining 6 dogs, in which veins were occluded to a segment of less than 3 feet (90 cm.), were all alive after an interval varying from three to five and one-half hours.

In several instances the pressure within the mesenteric veins to the loop of intestine selected was measured while a venous obstruction

was being produced. In each instance the pressure was seen to rise rapidly and quickly level off only slightly below the systemic arterial pressure. The fact that the venous pressure may rise to heights almost equivalent to the arterial pressure probably accounts for the rupture of the capillary bed of the wall of the bowel. There appears to be a direct correlation between the fall in blood pressure,

TABLE 6.—*Changes in Blood Pressure Produced by Various Types of Strangulation Obstruction of the Small Intestine*

Experi- ment No.	Weight of Dog Kg.	Length of Intestine Obstructed, Ft.	Time of Strangulation, Hr.	Initial Blood Pressure, Mm.	Resulting Blood Pressure, Mm.
Group 1: Encirclement of Pedicle					
5	20	1	4	...	140
14	5	1	5	...	140
1	11.3	1	3	...	100
2	16	1	4.5	...	130
3	9	1	5	...	100
8	11	3	4.25	...	130
7	20	3	4	...	110
47	8	4	5	110	90
9	19	5	4.5	130	100
11	10	5	3.75	...	94
13	8	4	4.5	...	110
32	..	4	5	...	90
13	10	5	4	...	90
10	5.5	5	4.5	...	80
31	..	7	7	...	120
36	25.5	11.5	4.5	...	70
Group 2: Ligation of Arteries and Veins					
17	20	4.5	4.75	...	120
16	14	5	4	...	145
16	14	5	6	...	135
115	18	2.5	18.5	...	20
115	18	2.5	19	...	Dead
116	22	2	18.5	...	70
116	22	2	20	...	Dead
Group 4: Ligation of Veins					
101	13.5	2	2	120	56
100	20	2.5	4	150	60
98	9	2.5	4.5	120	60
99	19	2.5	5.5	140	70
91	21	2.5	5	140	70
92	12	3	3	110	38
55	20	5	4	140	Dead
56	16.2	5	4	150	56
51	13	5.5	2.5	120	Dead
114	10	..*	1	140	Dead

\* In this animal the superior mesentary vein was ligated.

on the one hand, and the time, length and type of vascular occlusion, on the other. In general, the longer the time and the longer the loop strangulated, the greater the fall in blood pressure. The type of obstruction, however, is of even greater importance. In those instances in which the veins alone were ligated and in the strangulations involving encirclement (group 1), in which the arteries were not entirely occluded, the fall in pressure was much more rapid than in those instances (groups 2 and 3) in which the arteries were absolutely occluded, with or without occlusion of the veins.

*Period of Survival After Various Types of Obstruction.*—The four usual types of obstruction were produced in a number of instances with a view to determining the average length of life in the various groups. The lengths of bowel strangulated were varied in order to determine the variations which might result in accordance with the observations of Foster and Hausler.<sup>9</sup> In the experiments of group 1, in which an encircling ligature was placed about the mesentery and bowel in 14 dogs, the period of survival varied between four and twenty-eight hours. The mean length of life was sixteen hours. The length of bowel strangulated varied between 1 and 5 feet (30 to 150 cm.). The dog with the shortest obstruction lived the longest, an observation which is in accordance with Foster and Hausler's views. However, the dog with the longest obstruction lived longer than a number of other dogs with shorter obstructions. This and other exceptions to Foster and Hausler's conclusions were anticipated in view of the fact that the relative degree of arterial and venous obstruction could not be accurately controlled in this group. Further, the animals varied in weight as well (10 to 25 Kg.). Therefore, the actual length of intestine obstructed gives no indication of the relative amount obstructed, which is actually of greater significance. In 18 experiments of group 2, in which the arteries and veins were completely ligated, the shortest period of survival was eleven hours and the longest thirty-two. The length of intestine strangulated varied as in the preceding group between 1 and 5 feet (30 to 150 cm.). The mean length of life for this group was nineteen hours. In group 3, in which the arteries were tied in 9 dogs, the shortest period of survival was fifteen hours and the longest twenty-four hours. The length of bowel strangulated varied between 1 and 4 feet (30 to 120 cm.). The mean length of life was twenty hours. In group 4, in which the veins were tied in 15 animals, the shortest period of survival was two and one-half hours. The length of intestine varied between 3 and 5½ feet (90 to 170 cm.). The mean length of life was five and one-half hours.

Examination of table 7 reveals that the length of life in group 4, in which venous obstruction was produced was approximately one-fourth that in group 3, in which the arteries were obstructed, and in group 2, in which combined ligature of arteries and veins was performed; it was approximately one-third that of group 1, in which the degree of arterial occlusion was not absolute in all cases. Although the length of bowel involved is of great importance in shortening or prolonging the period of survival after strangulation obstructions, the type of obstruction seems to be of even greater significance, as a pure venous obstruction causes death in one-fourth the time that an arterial obstruction does.

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9. Foster, W. C., and Hausler, R. W.: Studies in Acute Intestinal Obstruction: II. Acute Strangulation, *Arch. Int. Med.* **34**:697 (Nov.) 1924.

*Loss of Blood in the Various Types of Intestinal Strangulation.*—The data presented here on losses in the blood volume were obtained from experiments on 38 animals. As in the other phases of this work, the usual four types of intestinal strangulation were employed. At necropsy, in each instance, the peritoneal fluid was measured, the strangulated loop with its contents weighed, the contents removed and the intestine reweighed. The length of the strangulated bowel was measured just prior to the strangulation and in some instances afterward as well. The amount of blood lost was calculated as being equivalent

TABLE 7.—*Period of Survival After Strangulation Obstruction of the Small Intestine in Dogs*

	Number of Experiments	Length of Strangulated Intestine, Ft.	Average Period of Survival, Hr.
Group 1 (encirclement of pedicle).....	1	1	28
	1	2½	18
	4	3	10
	1	3½	18
	5	4	14
	1	4½	18
	1	5	18
Group 2 (ligation of arteries and veins).....	4	1	23½
	6	2	21
	3	3	18
	3	4	16
	2	5	13
Group 3 (ligation of arteries).....	1	1	18
	3	2	21
	1	2½	18½
	3	3	22
	1	4	15
Group 4 (ligation of veins).....	5	3	7½
	1	3½	3½
	1	4	4
	2	4½	4¾
	5	5	6½
	1	5½	2½

to the peritoneal fluid plus the increase in the weight of the intestine over the calculated normal weight. That these figures give an estimate of the true loss of blood in groups 1 and 4 is evident from the results described in the preceding paragraphs. The loss in the blood volume was then calculated from these figures, the total blood volume being based on the arbitrary figure of 7.5 per cent of the body weight given by most authors as the average. In group 1 (strangulation by encirclement), in which there was only partial arterial occlusion and the loop was resected before the animal died, the loss in the blood volume varied from 20 to 50 per cent, with an average of 35 per cent for the entire group.

In groups 2 and 3, in which there was complete arterial occlusion, there was no increase in the weight of the strangulated loop over the

normal value. Consequently no values for increase in the weight of the intestine are listed for these two groups. In the instances in which the loop was ruptured, the peritoneal cavity contained large amounts of peritoneal fluid of high total protein content, the values ranging from that of the animal's own blood plasma up to twice that amount. In a few instances in which the loop was not ruptured the peritoneal fluid had a total protein content less than that of the blood plasma. The amount of fluid noted in the peritoneum was calculated to be 22 per cent of the total blood volume in the second group and 20 per cent in the third group.

In group 4 (venous ligation), symptoms of shock resulted relatively early and were soon followed by death. Within two hours, the animals began to show a definite increase in the respiratory and cardiac rates, and

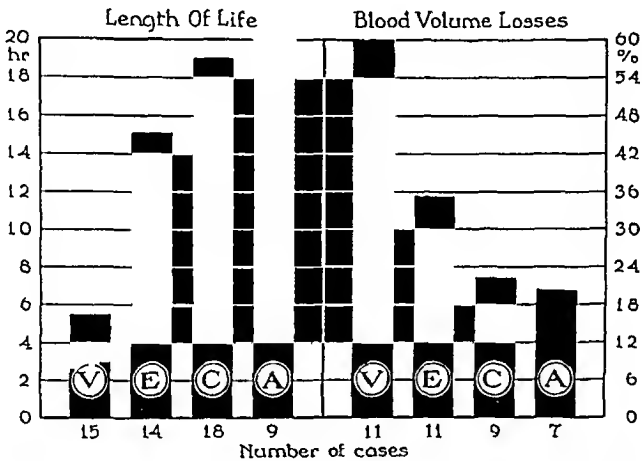


Fig. 5.—The correlation between loss of blood volume and length of survival in dogs with the various types of strangulation obstruction; *V* = venous; *E* = encirclement; *C* = complete; *A* = arterial.

the hemoglobin content had begun to fall, as had the blood pressure. In a few animals in which the abdomen was opened after this interval, the strangulated intestine was seen to be of a dark mahogany color, lusterless and distended, as previously reported. All these conditions were minimal shortly after the strangulation was produced and increased during its course, reaching a maximum at the time of death. Deaths in group 4 occurred after a loss of from 34 to 66 per cent of the total blood volume. The average for the group was 55 per cent, and the average length of life was five and one-half hours. Losses in the blood volume were calculated as in group 1. A summary of the data will be found in table 8. The rapid fall in blood pressure, early shock and death in group 4 (venous obstruction) were associated with a loss of

blood sufficient in itself to produce these results. The same is true of group 1 (obstruction by encirclement). The results obtained in groups 1 and 4 therefore confirm the work of Blalock,<sup>5</sup> who contended that the fall in blood pressure in shock is due to significant losses in the blood volume. In groups 2 and 3, in which the arteries were ligated, some factor other than loss of whole blood apparently enters in to play the major role in the causation of death.

#### INTERPRETATION OF RESULTS

The preceding experiments illustrate that strangulation obstruction, like intestinal obstruction in general, is not a distinct disease. The train

TABLE 8.—*Losses in the Blood Volume in Thirty-Eight Dogs With the Various Types of Strangulation Obstruction*

	Weight of Dog, Kg.	Length of Intes- tine, Ft.	Time of Strangu- lation, Hr.	Perito- neal Fluid, Cc.	Weight of Intes- tine, Gm.	Normal Weight of Intes- tine, Gm.	Per- centage Increase in Weight of Intestine	Total Loss of Blood, Gm.	Percent- age of Loss in Blood Volume
Group 1									
Minimum	8	3.0	2.6	30	240	76	133	180	20
Maximum	21	3.0	5.6	140	675	150	320	635	50
Average	15	3.2	4.0	82	460	103	235	425	35
Group 2									
Minimum	5	1.0	15.0	40	...	...	...	...	8
Maximum	14	5.0	32.0	325	...	...	...	...	48
Average	9	2.5	20.0	142	...	...	...	...	22
Group 3									
Minimum	8	1.0	15.0	40	...	...	...	...	14
Maximum	20	4.0	24.0	350	...	...	...	...	30
Average	15	2.5	20.0	259	...	...	...	...	20
Group 4									
Minimum	8	3.0	2.5	30	260	90	150	260	34
Maximum	22	5.5	12.0	300	1,030	170	490	1,015	66
Average	15	4.3	5.5	96	690	135	283	643	55

of symptoms, the development of shock and finally the ensuing death depend on at least three factors:

1. Loss of blood into the wall of the bowel, the lumen and the peritoneal cavity.
2. Transudation of plasma into the general peritoneal cavity.
3. Absorption of bacterial "toxins."

The course taken in any strangulation will depend on the relative degree of venous or arterial occlusion. If arterial occlusion predominates, the resulting pathologic picture will be an anemic (in the case of an absolute vascular occlusion, which probably occurs only in massive arterial thromboses) or hemorrhagic necrosis without marked distention of the lumen or the wall of the bowel. In these instances there will be an outpouring of plasma from the surrounding peritoneal surfaces in an attempt to rid the peritoneum of the gangrenous bowel.



Death will occur relatively late and will be secondary to a loss of plasma into the peritoneal cavity and an absorption of bacterial toxins therefrom. If, on the other hand, the venous occlusion predominates in the face of normally patent, pumping arteries, or even partially patent arteries, the result will be a loss of whole blood into the wall and lumen of the bowel and a transudation of plasma into the peritoneal cavity, associated with a distention of the strangulated loop, varying from a moderate to a marked degree.

Of clinical interest is the fact that shock and death result early after pure venous obstruction only when the strangulated intestinal loop is adequately long, or when no egress of blood can take place into the lumen of the adjacent normal bowel to relieve the intraluminary pressure of the strangulated loop. In many clinical cases, an egress of blood does occur into the normal adjacent bowel, and the rate at which blood is lost most likely depends on the degree of obstruction of the lumen of the bowel and on the resulting intraluminary pressure.

#### SUMMARY

The results of 240 experimental strangulation obstructions are herewith presented. They seem to show that a loss of whole blood and plasma is an important contributing factor to the development of shock and even of death. The gross pathologic picture, as well as the microscopic observations, indicates a loss of whole blood into the wall and lumen of the strangulated loop of the bowel.

The type of strangulation produced is found to be dependent on the relative degree of venous or arterial occlusion. When venous occlusion predominates the loss of whole blood is the chief factor, and when arterial occlusion predominates the loss of plasma is important. Tables are presented which show that there is a marked increase in the weight of the strangulated bowel over the normal weight. This increase in weight has been found to be due to the accumulation of blood in the wall and lumen of the strangulated loop of the bowel. Determinations reveal that the material within the loop has a high hemoglobin content and that the free peritoneal fluid is similar in total protein content to the animal's own blood plasma.

The loss of blood in strangulation obstructions has been calculated and found adequate, with the venous types of occlusion at least, to account for the shock and death which occur. Experiments presented tend to show that the blood pressure falls rapidly and the hemoglobin content drops rather uniformly. Experiments are also presented which show that the fall in blood pressure depends on the length of intestine involved and on the predominate type of strangulation produced.

Experiments are presented to show that "toxic products" are not present in the peritoneal fluid except terminally when the loops are

gangrenous or ruptured. Histamine, strychnine and tetanus toxin have been introduced into strangulated loops in order to test the absorption of these products. Practically all the tests failed to reveal any evidence of the absorption of these products except terminally, when the loops were gangrenous or ruptured. Experiments are also presented which tend to show that the intestinal wall per se is not toxic.

The only evidence of toxic absorption is found late in the course of any strangulation obstruction and is apparently due to the presence of innumerable bacteria in the peritoneal cavity. The effect of the bacteria is apparently quantitative, as gross perforation of the intestine is essential to a lethal issue when the peritoneal fluid is tested by introducing it into the peritoneal cavity of a normal animal.

#### CONCLUSIONS

1. There is little or no evidence for the direct absorption of "toxic products" from strangulated loops of intestine.
2. There is little evidence for the transperitoneal absorption of "toxic products," except late in the course of strangulation obstruction, when the wall of the bowel is no longer viable.
3. Whole blood and plasma are apparently lost from the general circulation in quantities sufficient in themselves to account for the symptoms of shock and death which occur in most cases of strangulation obstruction.

# OSTEOGENIC SARCOMA

## A REPORT OF TWO UNUSUAL CASES

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I have been fortunate in observing two interesting cases of osteogenic sarcoma in the past five years, and I submit the records in detail:

### REPORT OF CASES

CASE 1.—J. S., a girl aged 13, was first seen in April 1932. The mother stated that several months previously her daughter had fallen, striking her right knee. Sometime later the child began to limp and to complain of pain in the leg. A swelling appeared above and to the outer side of the knee, and the patient was taken to the General Memorial Hospital where she was examined. A diagnosis of osteogenic sarcoma was made, and the family was advised that an amputation was imperative. The parents refused to consent, and a short while later the child was brought to my office.

After having some roentgenograms taken, I made a diagnosis of osteogenic sarcoma and advised amputation (fig. 1). A second refusal led me to plead for local excision, and this was granted. Part of the growth was removed at the Columbus Hospital Extension on May 23, 1932, and the pathologic report of Dr. A. Sala stated that the growth was a rapidly growing osteogenic sarcoma.

Still the family refused consent for an amputation. My only recourse, in the hope of retarding the growth, was to give a series of injections of Coley's toxin. Injections were given locally and in the buttocks for nearly a month, but were of no avail. The pain and limp increased, and the growth soon reappeared locally.

A roentgenogram at this time showed the growth to be as large, as ever (fig. 2). Finally the parents consented to an amputation, which was done through the upper third of the thigh on July 17, 1932, at Bellevue Hospital.

The pathologic report, made by Dr. McWhorter, was as follows: "The specimen consists of the lower end of the femur, which has been split longitudinally (fig. 3). On the popliteal surface, just proximal to the epiphysial line, is a fusiform growth of dense consistency. This growth involves the medullary cavity and appears to be growing outward. Microscopic examination shows a densely infiltrating mass of undifferentiated connective tissue cells of short spindle type. Scattered throughout the sections are many giant cells of tumor type" (fig. 4).

Since the operation the patient has slowly recovered, but she has been kept under observation. She has not gained much weight, but periodic roentgenograms of her chest and long bones show no metastases. During the past year she has had

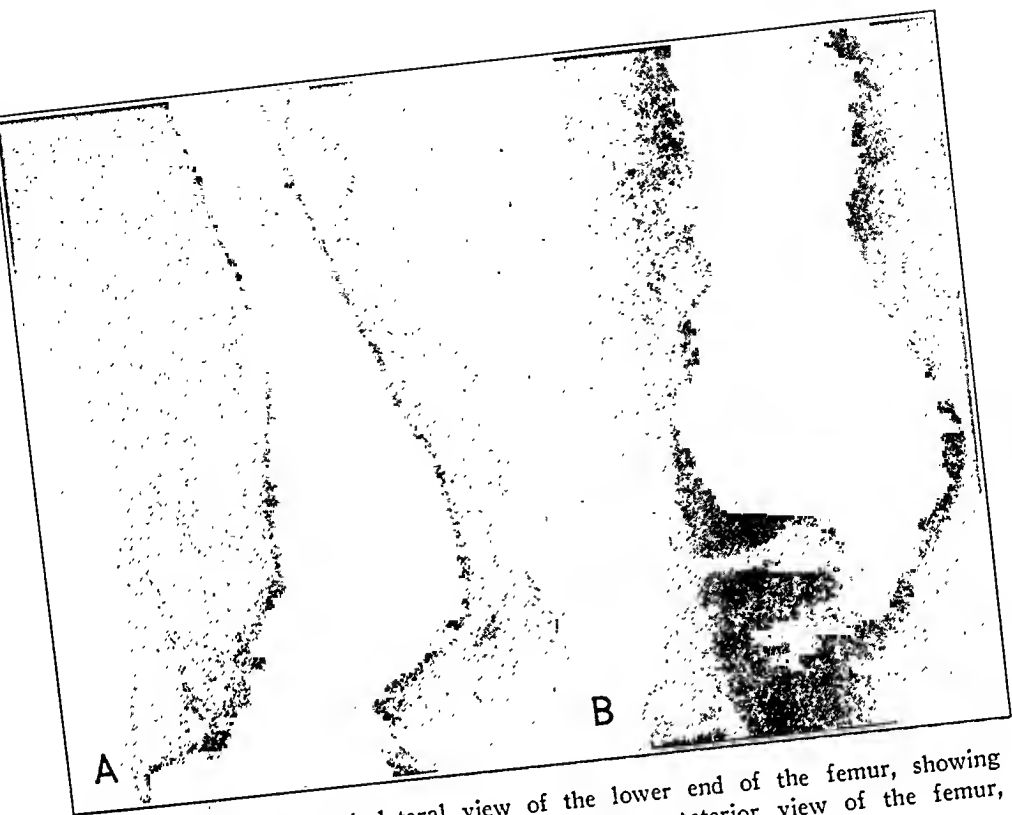


Fig. 1 (case 1).—*A*, lateral view of the lower end of the femur, showing growth that involves the periosteum. *B*, antero-posterior view of the femur, showing characteristic sun ray bony spicules.

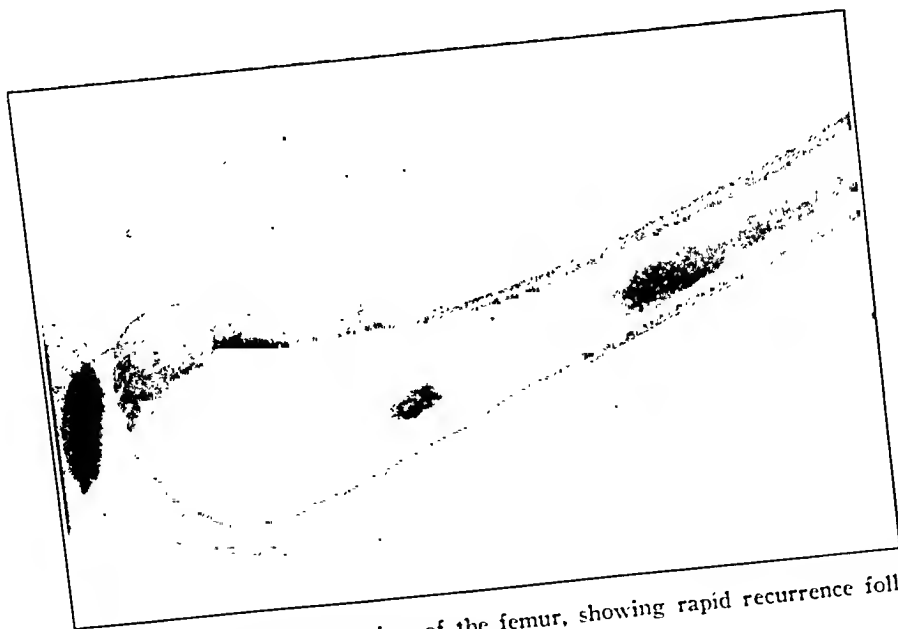


Fig. 2 (case 1).—Lateral view of the femur, showing rapid recurrence following curetting.

trouble with her stump. It has become quite swollen, and she has not been able to wear any artificial limb. A plastic revision was done in April 1936, and a fairly large slice of skin and fat was excised. No evidence of any soft local tumor recurrence was found.



Fig. 3 (case 1).—Cross-section of the specimen.

CASE 2.—E. D., a boy, a patient of Dr. D. Zetena, was admitted to the Columbus Hospital Extension Nov. 26, 1934, and was discharged Jan. 27, 1935.

The history given was that while passing through a door of a train on Sept. 30, 1934, the child was pushed by the crowd so that his right foot was caught between the platform and the train and he fell onto the platform, striking his right thigh. From that day on he complained continuously of pain, and his mother noticed a swelling on the right thigh, which was soft, was not red and did not fluctuate.

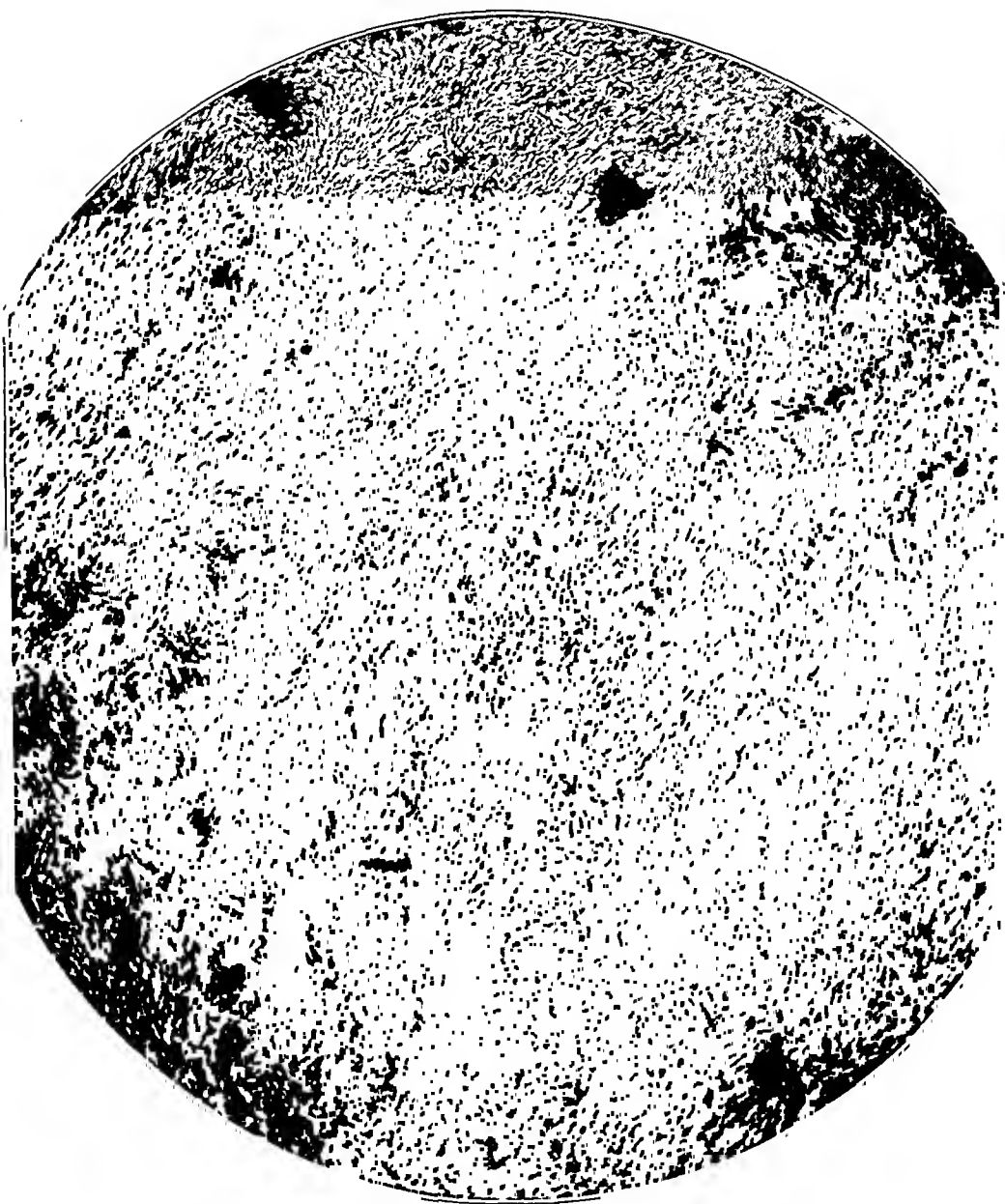


Fig. 4 (case 1).—Photomicrograph of osteogenic sarcoma of the thigh.

Physical examination revealed nothing abnormal except the painful swelling in the upper part of the right thigh. There had been no previous illnesses except pneumonia at the age of 8 months and otitis media at 1 year.

The blood count on admission showed 13,000 white cells, with 52 per cent lymphocytes and 37 per cent neutrophils. The urine was essentially normal.

Roentgen examination of the right femur showed slight irregularity of the periosteal shadow along the anterior and lateral borders of the upper third of the shaft of the femur, the changes beginning slightly below the greater trochanter and extending downward about 3 inches (9.5 cm.). The periosteum was slightly elevated in the upper and lower portions. There were fine radiating lines extending at a right angle from the cortex into the soft tissue. There was no definite



Fig. 5 (case 2) —Early osteogenic sarcoma with sun ray bony growth into the soft parts

involvement of the cortex or medulla. The changes had the appearance of a periosteal osteogenic sarcoma (fig. 5).

On Dec. 1, 1934, the patient was ready for disarticulation at the hip; so a preliminary histologic examination of a portion of the periosteum was made, and a frozen section showed a sarcoma. Thereupon disarticulation was carried out.

Two curved incisions were made starting about the center of Poupart's ligament, one going outward and the other inward, both meeting behind near the middle of the gluteal fold. The femoral vessels were exposed and doubly ligated with chromic catgut. The adductor and abductor muscles and hamstrings were severed close to their origin. An injection of 90 per cent alcohol was made into the sciatic nerve, as located, and the nerve was cut high up. The capsule of the joint was incised, the ligamentum teres clamped and divided and the head of

the femur disarticulated. The joint cavity was then thoroughly curetted. All excess muscle was excised, and the rest was approximated by loose interrupted catgut sutures. A drain was introduced down to the acetabulum, and the skin flaps were brought together by interrupted silk sutures.

The patient had moderate fever and was given three transfusions, one of which was necessitated by a fall soon after he began to walk. This fall resulted in a



Fig. 6 (case 2).—Cross-section of the femur, showing osteogenic growth.

slight hemorrhage from the stump. Fifty-seven days after operation the patient was discharged with the stump well healed.

The pathologic report, made by Dr. A. Sala, was as follows: "The upper third of the femur is the seat of a periosteal tumefaction growing outward into the soft tissues (fig. 6). Spicules of bone are palpable, projecting from the periosteum. The upper half of the femur is yellowish in whorls, suggesting neurogenic sarcoma; the lower half is soft and fleshy and grayish. The microscopic diagnosis is osteogenic sarcoma arising from the periosteum."



## COMMENT

The first case is reported because of the extraordinary fact that after a rapid local recurrence of the growth following the initial operation, and after repeated injections of Coley's serum which did not help the condition, an amputation was done. At the present time, after an interval of five years, there has been no reappearance of the tumor in the stump or in any other part of the body.

The second case is of interest in view of the fairly definite history of trauma, the uncommon location of the growth and the fact that the child could stand the shock of a radical disarticulation of the hip. This patient has gone over two years without recurrence or metastases.

# DUGAS ON THE CURABILITY OF INFLAMMATION

CECILIA C. METTLER, A.M.

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Dr. Louis Alexander Dugas (1806-1884) held the Chair of Surgery at the Medical College of Augusta (the present University of Georgia School of Medicine) from 1855 to 1882, was dean for a period of twenty years and was editor of the *Southern Medical and Surgical Journal* from 1851 to 1858. Eponymously he is remembered for his famous sign indicative of dislocation of the shoulder joint. During his professional career he published approximately one hundred articles, which are a credit to his surgical versatility and to the wide range of his medical knowledge. The paper which follows is one of several Dugas manuscripts which have recently come to light.

## REMARKS ON THE CURABILITY OF INFLAMMATION

BY L. A. DUGAS, M.D.

(Read before the Augusta Library and Medical Society, Sept. 3, 1875.)

What is inflammation?—If we look to Erichsen for a reply we find that "the study of the inflammatory process is one of the most complex and difficult on which the surgeon can enter; but the labor required to master its details is well bestowed, inasmuch as an acquaintance with its nature, symptoms and progress, gives an insight into a greater part of the Science of Surgery."

He then adds: "Yet as the discussion of this subject belongs rather to the domain of General Pathology than to that of Practical Surgery, it cannot consistently be entered upon here" (p. 87-Am. Ed.-1869).

Turn to Gross (p. 49, 1872) and you find that "inflammation may be defined to be a perverted action of the capillary vessels of a part, attended with discoloration, pain, heat, swelling and disordered function, with a tendency to effusion, deposits or new products. In addition to these changes, there is also an altered condition of the blood and nervous fluid, as an important element of the morbid process. In what inflammation essentially consists, it is as impossible to determine as it is to explain the intimate character of attraction, repulsion, gravitation, or cohesion."

Hear Ashurst: "Authors, though differing as to the proper explanation to be given of many of the phenomena of inflammation, are, I think, generally agreed that those phenomena are mere modifications of the phenomena of natural textural life." (p. 34).

It is not necessary to multiply references to authorities, for this would be simply to make confusion worse confounded. No attempt at a mere definition of inflammation can be successful. We must first recognize and study the funda-

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From the Department of Anatomy, University of Georgia School of Medicine.

mental physiological functions of the body, that is to say, Innervation, Capillary Circulation, Nutrition and Secretion, and we shall find that inflammation always involves a deviation from the normal condition of every one of these functions.

While there may be lesions of any one of these functions, or of several of them, without inflammation, this *always* exists when the whole are affected. And yet inflammations are not always alike; they differ infinitely according to their cause and to the structure invaded.

Inflammatory affections, so called, are therefore as numerous and as various as the diseases classed under this head. No two are alike in their manifestations, nor in their history. They differ in causation, in symptoms, in duration, in terminations and in curability. They are therefore strictly speaking, entities; and should be more generally admitted to be so. If this general assent could prevail we might dispense with the word inflammation, and allow each entity or disease to be judged and treated according to its own or individual peculiarities. But the word has been so long in use, and is so intimately interwoven with our facts as well as theories, that we may not expect to see it set aside in our generation, nor probably in several more of them. With this explanation, I will continue its use as a matter of convenience whenever it answers the purpose.

Is inflammation curable?—This may strike some as a ridiculous question, for it is in striking contrast with the dogmatic declarations of every period of the history of medicine. To intimate any doubt as to the efficacy of the modes of treatment advocated by leading men from Hippocrates to Broussais, would seem to be as preposterous in Medicine as heresy in theology. And yet the extravagancies of Broussais aroused a spirit of inquiry so potent that he lived to see his favorite dogmas, first doubted, and then almost unanimously discarded by the profession. His hobby that by depletion all inflammations could be readily “removed,” has now become obsolete, and every one knows that you may draw blood “*ad deliquium animi*” without curing a simple pimple on the face, and that the same inefficiency attaches to any other form of antiphlogistic treatment. I wish it to be borne in mind that I use the term *cured* in its strict sense; that is to say, that the inflammatory process was found to pursue the even tenor of its way in despite of any known form of treatment.

As it was my good fortune to be at the seat of war whilst it progressed most furiously between the friends and adversaries of the Broussaisian School, I had abundant opportunities to verify the claims of the respective parties; and became satisfied that the victory was with the opposition, and that inflammation could not be *cured* by antiphlogistics, nor by any other plan of treatment then known. Whenever the inflammation was on the surface, so as to be seen in its various stages, it was never arrested by treatment; but ran its peculiar regular course to resolution or to some other of its accustomed terminations. Such being the case with regard to inflammations subject to ocular inspection, we could not reasonably suppose different results in the progress of inflammations affecting internal organs.

Such are the doctrines I continued to teach until about ten years ago; and the object of this paper is to lay before you how my views have undergone a change.

As far back as the introduction of Quinine in the treatment of our malarial fevers, which were then considered inflammatory, and treated as such, I was forcibly impressed by the prompt and certain arrest of the disease by this wonderful agent. Could it be that quinine arrested inflammation?—or had we been in error with regard to the pathology of our fevers?—The organs apparently implicated were out of sight, and we might have mistaken hyperaemia for inflammation. I became convinced that such was the fact, and the efficacy of Quinine

was to be found in its effect on the nervous system, the blood, and the capillary circulation in general; thus bringing about an equalization of circulation and relief of *congestion*—not *inflammation*. There is no lack of evidence that by the timely use of quinine we may *prevent* the development of inflammation in cases in which this would probably have occurred without it. We have also strong reasons for believing that quinine may modify the progress of inflammatory action after its occurrence. But I have yet to see a case in which inflammation once set up, has been “jugulated” by quinine. It is true that quinine exerts a most beneficial effect upon Pneumonia and Dysentery as they prevail in this section of the country, and that it is really our sheet-anchor in these affections. But this is so because our forms of pneumonia and dysentery, especially when epidemic, are almost invariably mixed with malarial or paroxysmal fever, which readily yields to quinine, and leaves the inflammatory complication to subside gradually under judicious management.

About ten years ago I found that by applying Tincture of Iodine to a furuncle the progress of inflammation was arrested and it terminated by resolution. Repeated trials were attended with similar results. If applied even so late as the formation of the core, the pain would cease, the swelling would subside, and the core would come away in due time. You know that furuncles are of two kinds, the one simple and the other preceded by a vesicle, and therefore called the vesicular. From the resemblance of the latter form to carbuncles, I formerly designated them as *carbuncular furuncles*, but now prefer to call them *vesicular furuncles*, because this indicates their anatomical peculiarity. Moreover, carbuncles never begin with a vesicle. Vesicular furuncles are much more slow, painful and extensive than simple furuncles, and have a predilection for the back of the neck, where they are frequently mistaken for carbuncles. If you will closely examine them in the initial stage, you will scarcely ever fail to detect a vesicle about the size of a pin-head, attended with itching, and subsequently with tumefaction and pain. The vesicle is soon rubbed away by attempts to relieve the itching. The vesicle does not reappear, but the inflammation extends through the skin into the subjacent tissue, terminating in suppuration and sloughing.

Now if you apply the Tincture of Iodine to such cases in any stage you may safely expect to put a stop to any further inflammatory action. Both pain and tumefaction will readily subside and the trying use of the knife be obviated.

I have never had an opportunity to test the efficacy of this treatment in genuine carbuncle; but am strongly disposed to think it might be equally beneficial as it is in furuncles.

But a much more useful application of this treatment is to be found in Erysipelas, especially when consequent upon traumatic causes. The relief in such cases is sometimes so prompt as to partake of the marvelous. The last case I treated was that of a man who had sustained an injury to one of his fingers and came to me with the whole hand greatly swollen, red and painful, with rapidly spreading erysipelas. I immediately gave the entire red surface a thorough painting with Tincture of Iodine, and advised its repetition in 6 and 12 hours. He visited me after the third painting, and I found the tumefaction much reduced, no pain, no tendency to spread, and every indication of the rapid subsidence of the disease. He was advised to use the application only morning and night, and was well in a few days. This plan of treatment may be regarded as specific, when resorted to sufficiently early and in the proper way.

For furuncles and erysipelas I usually direct the painting to be effectually done morning and night, in bad cases three times a day, and gradually discontinued as the disease disappears. In the sub-cuticular and sub-cutaneous forms of whitlow

I have found Tincture of Iodine sometimes beneficial, but not so in the thecal and periosteal varieties. For buboes, whether syphilitic or otherwise, I have no reason to think it prevents or lessens the tendency to suppuration; indeed I am rather disposed to think I have seen suppuration oftener when it was used than when I resorted to other expedients. This may appear singular when we remember how valuable an agent the Tincture is in dispensing some of the chronic enlargements of lymphatic glands.

We have endeavored to demonstrate; first, that no *definition* of the word inflammation hitherto proposed is satisfactory.

Secondly, that the so-called inflammation is a radical perturbation of the fundamental physiological functions, which varies according to its cause and the tissues involved;

Thirdly, that inflammations should be regarded and treated as entities, or distinct diseases;

Fourthly, that when I commenced my professional studies it was generally conceded that inflammatory affections were curable;

Fifthly, that the ultraisms of Broussais instigated a spirit of inquiry which resulted in the conviction that no treatment then known could be said strictly to cure or to arrest the regular progress of inflammatory action;

Sixthly, that this conviction became, with me, somewhat shaken by the introduction of quinine;

And finally, that it is now demonstrated beyond doubt that some of the forms of inflammation may be effectually arrested by the application of tincture of iodine to the affected locality.

It has been wisely stated that there is nothing new under the sun, and I shall therefore not lay claims to originality which might be controverted by the more erudite; but I must say that my first use of Tincture of Iodine, as above narrated, was not instigated by knowledge derived from others—If others had done the same before I was not aware of the fact.

I have ventured to place this paper at your disposal because I regard the discovery—by whomsoever made—of the fact, that some forms of inflammation are undoubtedly curable, as one of the utmost importance. It not only corrects one of the convictions of the learned, but must lead to farther discoveries in the same direction. As one step in advance is only the precursor of others, let us redouble our exertions, in the hope that some one among us may have the honor of contributing the next fact.

## PARTIAL CHOLECYSTECTOMY

W. L. ESTES JR., M.D.  
BETHLEHEM, PA.

The treatment for acute suppurative or gangrenous cholecystitis has recently been given renewed consideration. The controversial question has again been raised of immediate or early operation as against delay in operation, because the mortality following early operation has seemed to be lower than that following routine operative delay (Heuer). The operation of choice for acute or chronic cholecystic disease is removal of the gallbladder. One may expect a high mortality if cholecystectomy is invariably used on patients who are extremely ill or who are bad risks, and for such patients cholecystostomy, which is merely a palliative procedure in from 25 to 30 per cent of cases, must be resorted to. The likelihood that cholecystectomy must be performed subsequent to cholecystostomy because of recurrent symptoms or a persistent biliary fistula makes primary cholecystectomy particularly desirable. In cases of supuration, cholecystectomy from above downward often proves to be easier. But when there is massive inflammation and induration about the cystic and common ducts, any type of complete cholecystectomy may be not only technically difficult but attended with difficulty in controlling hemorrhage and accompanied by an unduly high mortality. It is particularly for this type of severe suppurative or gangrenous gallbladder that the procedure of partial cholecystectomy has been found to be exceedingly valuable.

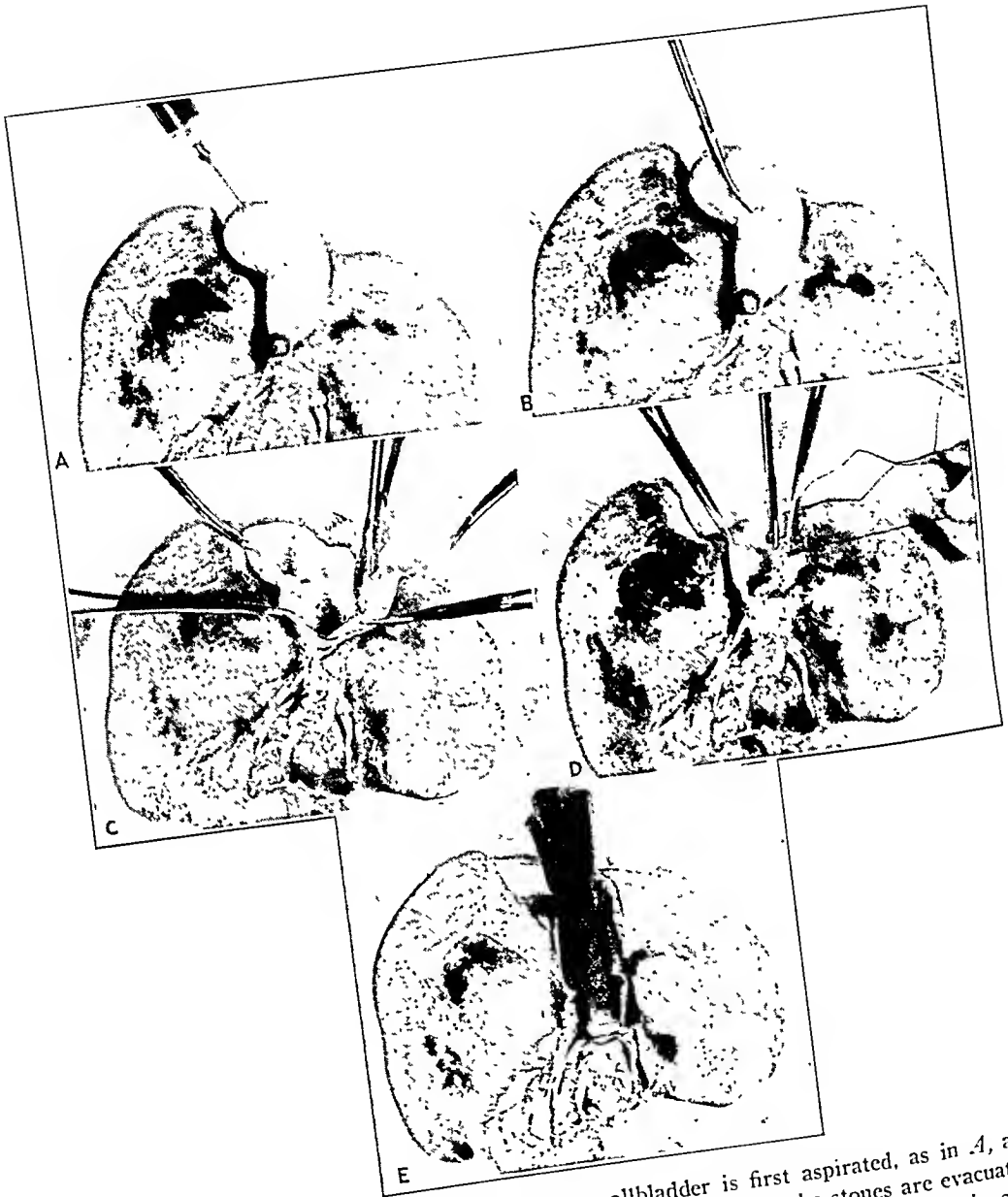
### OPERATIVE PROCEDURE

The operative technic follows:

The gallbladder is exposed by an incision through the upper right rectus muscle or one parallel to the costal margin. The area involved is isolated by gauze packs, and the adhesions to the gallbladder are freed. The gallbladder is aspirated of its fluid contents, as shown in *A* of the accompanying illustration. The fundus is incised, the stones are removed and the gallbladder is dried with gauze and swabbed with tincture of iodine; it is then split down with scissors to within from 1 to 2 cm. of the cystic duct, as in *B*; this often facilitates the removal of a stone impacted at the junction of the ampulla and the cystic duct which cannot be evacuated otherwise. The gallbladder is partially removed by trimming off the redundant part of each half down to the border of the fossa of the liver, that portion which is attached to the liver being left, as in *C*. The bleeding from these cut edges is controlled by

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Read before the Section on Surgery, General and Abdominal, at the Eighty-Eighth Annual Session of the American Medical Association, Atlantic City, N. J., June 10, 1937.



Steps in the operative technic. The gallbladder is first aspirated, as in *A*, and the fundus is incised, as in *B*. After the fundus is incised, the stones are evacuated, the gallbladder is dried out and swabbed with tincture of iodine and is split down to the cystic duct. After the removal of any stone at the junction of the ampulla and the cystic duct, the redundant portion of each half is trimmed off with scissors, leaving only that portion of the gallbladder attached to the liver, as in *C*. The cut margins of this remnant of the gallbladder are sutured with a lock stitch, as in *D*. Cigaret drains are placed about the cystic duct and against the remnant of the gallbladder to hold it open, as in *E*.

ligature or lock stitch up each side, as in *D*. Two or three cigaret drains are placed about the cystic duct and brought out against the remnant of the gallbladder to hold it open, as in *E*. A tube may be placed at the opening of the cystic duct, which is not ligated or tied off in any way. The greater omentum or the thickened plastic gastrocolic omentum is placed against the drains to separate them from the nearby viscera. The drains are brought out either through the operative wound or through a lateral stab wound directly over the remnant of the gallbladder, and the wound is closed.

I have used pure phenol or actual cautery in a few cases instead of tincture of iodine to destroy the mucous membrane of the remaining bit of gallbladder. But having found that there was no evidence of reformation of the gallbladder in the early cases in which iodine was used, I have recently uniformly applied it to avoid the possibility of prolonging the convalescence by the development of an eschar or necrosis, as in one case in which cautery was employed.

#### INDICATIONS FOR THE OPERATION AND MORTALITY

In 1929 I described this operation and reported the end-results in seven cases.<sup>1</sup> I have now employed it in forty-eight cases over a period of fourteen years. In forty-four cases it was used because of an acute suppurating or gangrenous gallbladder with induration about the cystic and common ducts. In four, it was used because of extremely difficult exposure of a small contracted gallbladder which was densely adherent to the liver.

There has been one death, a mortality of 2.08 per cent. This fatality occurred in a woman 65 years of age with advanced myocardial disease and a large gangrenous gallbladder. She had recovered, apparently, and was about to be discharged from the hospital on the sixteenth post-operative day, when a large pulmonary embolus developed.

#### FOLLOW-UP STATISTICS

A careful personal follow-up examination has been obtained on all but five patients, i. e., on forty-two.

*Relief from Symptoms.*—Thirty-four patients (81 per cent) have remained well and free from any complaint referable to the gallbladder, the longest for twelve years. Five (11.9 per cent) require a slight dietary restriction, a diet low in fat, because of occasional bloating and belching after meals. No biliary fistulas have occurred, and no operation has been performed for recurrent disease of the gallbladder. Frequently, after the third or the fourth postoperative day there was a free discharge of bile, but the sinus healed readily after the drains were removed.

*Subsequent Involvement of the Common Duct.*—Three patients (7 per cent) have required operation for stones in the common duct six, eight and nine years, respectively, after partial cholecystectomy.

1. Estes, W. L., Jr.: Partial Cholecystectomy, Arch. Surg. **23**:119 (July) 1931.



Also, two of the five patients requiring dietary restrictions have had transitory symptoms of jaundice, epigastric pain and vomiting at long intervals. One of these has remained free from symptoms for eight years and now has diabetes. Another patient had ten stones removed from the common duct coincident with partial cholecystectomy, but as a rule simultaneous exploration or operation on the common duct is rarely advisable when extensive induration and inflammation are present about the duct because of the added operative risk and excess trauma due to the technical difficulties of exposure and control of hemorrhage and infection. Ordinarily, if the involvement of the common duct is definite at the time of partial cholecystectomy, a two stage procedure had best be planned.

3. *Fate of Remnant of Gallbladder Allowed to Remain.*—I have had the opportunity to reoperate on three patients. Two required hysterectomy, and the area of the gallbladder was simply palpated. There were dense adhesions to the fossa of the gallbladder, but no evidence of any thickening to suggest reformation of the gallbladder. The third patient had to undergo choledochostomy for the removal of 5 stones eight years after the partial cholecystectomy. There were adhesions of the gastroduodenal omentum and thickening of the capsule of the liver over the fossa of the gallbladder but no vestige of anything that even resembled the gallbladder or a remnant of the gallbladder.

*Postoperative Hernia.*—As extensive drainage is necessary in partial cholecystectomy—at least three drains are usually required—postoperative hernia might readily be expected, except in those cases in which the drains are brought out through a lateral stab incision. In my series of cases, an opening in the fascia at the point of drainage could be palpated in most of the scars, but in only six of the cases (14.3 per cent) was there definite hernia—that in an obese man of 76 was large and gave symptoms of obstruction, but he has consistently refused operative relief.

*Miscellaneous.*—In three cases diabetes developed from three to eight years after operation. In one a keloid occurred in the scar. Six patients have died of disease unrelated to the biliary passages or liver from one and one-half to twelve years subsequent to operation.

#### REVIEW OF LITERATURE

Partial cholecystectomy is not a new procedure. In 1899 and again in 1900 W. J. Mayo<sup>2</sup> reported cases, particularly of obstruction of the cystic duct, in which the removal of stones and the mucous membrane

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2. Mayo, W. J., and Mayo, C. H.: A Collection of Papers, Published Previous to 1909, Philadelphia, W. B. Saunders Company, 1912, vol. 1, pp. 348 and 355.

of the gallbladder was done instead of complete cholecystectomy. Partial cholecystectomy was described in 1920 by Bengolea.<sup>3</sup> In 1921 Martin<sup>4</sup> cited five cases of acute cholecystitis in which he removed the stones, split the gallbladder and held it wide open with drains.

In 1923 de Martel<sup>5</sup> reported that in two of a series of fifty-two operations on the gallbladder in which it was difficult to separate the ampulla and the cystic duct from adjacent structures he split the gallbladder from the fundus to the ampulla, divided the cystic duct and cut away the free part of the gallbladder, swabbed the remaining portion with tincture of iodine and drained it. Both patients recovered.

In 1924 Zabala and Bengolea<sup>6</sup> cited four cases in which partial cholecystectomy was performed, with recovery; in one there was a mass of adhesions about the gallbladder; in another a calculus was impacted in the cystic duct, which was firmly indurated and adherent to the common duct, and in a third a piece of the gallbladder was left near the cystic duct because of the friability of the tissue. They expressed the belief that the operation is indicated in cases of severe suppuration in which resection would be fatal. The gallbladder is split, and the stones are removed, after which the gallbladder is resected, the portion attached to the liver being left; the mucosa of this remnant is curetted, and tincture of iodine is applied.

Pauchet<sup>7</sup> decided that partial cholecystectomy is indicated (1) in the feeble or icteric patient with stones in the common duct and gallbladder; (2) in the patient with an atrophic gallbladder and stones; (3) in the patient with a subacute or acutely inflamed gallbladder adherent to the adjacent organs, and (4) in the patient with suppurative cholecystitis with fever. He expressed the belief that this operation avoids cholecystectomy at a time when complete cholecystectomy would give a mortality of 50 per cent. He followed Zabala and Bengolea's technique, except that the remaining mucosa is swabbed with ether as well as with tincture of iodine, and when there are strong adhesions to the nearby intestines, the gallbladder is freed from the liver and the portion adherent to the intestine is allowed to remain. The operation has been performed only in carefully selected cases in which routine cholecystectomy seemed to be indicated but would be a dangerous procedure because of technical difficulties or the amount of infection present.

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3. Bengolea, A. J.: *Bol. y trab. de la Soc. de cir. de Buenos Aires*, 1920, p. 285.

4. Martin, E. D.: *New Orleans M. & S. J.* **74**:204, 1921.

5. de Martel, T.: *Bull. et mém. Soc. de chir. de Paris* **49**:306, 1923.

6. Zabala, A., and Bengolea, A. J.: *Lyon chir.* **21**:281 (May 7) 1924.

7. Pauchet, V.: *Gaz. d. hôp.* **87**:1077, 1924.

In 1927 Gatch<sup>8</sup> and also Zimmerman<sup>9</sup> reported a similar technic.

In performing partial cholecystectomy for gangrenous cholecystitis, Haggard<sup>10</sup> (1930) destroys the mucosa of the remaining portion of the gallbladder either with phenol or with actual cautery, inserts a tube into the cystic duct for drainage and sutures the cut edges of the gallbladder over it.

McKenty<sup>11</sup> (1933), in reviewing the treatment for acute cholecystitis, cited thirty-three cases in which partial cholecystectomy was performed, with one death. After aspirating the contents of the gallbladder, he opens it, removes the stones and swabs the gallbladder with iodine, leaving an iodine pack in "the sac," and exposes and ties the cystic duct and artery. "The sac is then excised either from above downward or from below upward, leaving the portion attached to the liver undisturbed. From this portion the softened mucosa is easily removed by rubbing with gauze preferably saturated with iodine."

Ritchie<sup>12</sup> (1937), after splitting the gallbladder and excising the "wings," removes the mucous membrane of the portion allowed to remain, sutures a tube into the stump of the ampulla and cystic duct and closes the denuded fragment of the gallbladder by suture. He reported sixteen cases in which this procedure had been used, with no mortality.

#### SUMMARY

It must be understood that this operation would seem to be particularly applicable in cases of acute suppurative or gangrenous cholecystitis or empyema of the gallbladder, especially when there is induration about the cystic and common ducts, and occasionally for the small, densely adherent, thickened, atrophic gallbladder which cannot be easily separated from the bed of the liver. In no way should partial cholecystectomy be considered to supplant complete cholecystectomy when complete removal can be safely accomplished. The operator who is exceptionally skilful in the use of cholecystectomy from above downward may find less use for partial cholecystectomy than one whose proficiency has been directed to cholecystectomy from below upward. Furthermore, though cholecystostomy must still be reserved for the patient who is an exceptionally bad risk, fewer cholecystostomies seem indicated when familiarity with partial cholecystectomy has been acquired.

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8. Gatch, W. D.: *Tr. West. S. A.* **37**:345, 1927.

9. Zimmerman: *Tr. West. S. A.* **37**:341, 1927.

10. Haggard, W. D.: *Wisconsin M. J.* **29**:683, 1930; *Ann. Surg.* **105**:790, 1937.

11. McKenty, J.: *Canad. M. A. J.* **33**:771, 1933.

12. Ritchie, H. P.: *Surgery* **1**:581, 1937.

However, what would seem particularly to recommend partial cholecystectomy for acute suppurative cholecystitis is its low mortality. Postoperative mortality from this disease has been reported as 13.5 per cent by Miller,<sup>13</sup> 9.3 per cent by Smith,<sup>14</sup> 5.5 per cent by Graham,<sup>15</sup> 4.7 per cent by Judd and Phillips<sup>16</sup> and 3.2 per cent by Heuer.<sup>17</sup> Heuer, in advising the consideration of an early operation in cases of cholecystitis, especially has pointed out that operation before gangrene or perforation has occurred may play an important role in reducing the mortality. But none of my patients was admitted to the hospital within forty-eight hours of the onset of symptoms. They all received careful routine preoperative preparation and were operated on perforce, therefore not in the early stages of the disease. Partial cholecystectomy under these conditions, yielding a mortality of but 2.08 per cent, would seem to have a place in the treatment of advanced gangrenous or suppurative cholecystitis.

#### CONCLUSIONS

1. Partial cholecystectomy has and should have a very restricted field.

2. It should not be used when complete cholecystectomy can safely be performed.

3. It is particularly indicated: (*a*) in cases of acute gangrenous and suppurative cholecystitis when complete cholecystectomy is desirable but is technically impossible or unsafe, particularly with extensive induration and infiltration about the cystic and common ducts, and (*b*) in an occasional case of a contracted thickened gallbladder which is markedly adherent to the liver.

4. End-results in forty-eight cases would seem to demonstrate: (*a*) that partial cholecystectomy does act as cholecystectomy, i. e., no reformation of the gallbladder or stones occurs subsequently; (*b*) that it would seem to give end-results comparable to those for cholecystectomy in cases of cholelithiasis (81 per cent of patients completely well and 11.9 per cent well with dietary restrictions); (*c*) that postoperative involvement of the common duct may occur occasionally—7 per cent, and (*d*) that when carefully and reasonably employed, the operation is attended by a surprisingly low mortality.

#### ABSTRACT OF DISCUSSION

DR. WILLIAM D. HAGGARD, Nashville, Tenn.: The indications and contraindications for partial cholecystectomy have been well outlined. It is a *modus vivendi* remedy, designed to do away with the serious complications that occur after cholecystectomy of the gangrenous gallbladder.

13. Miller, R. H.: *Ann. Surg.* 92:644, 1930.

14. Smith, M. K.: *Ann. Surg.* 98:766, 1933.

15. Graham, H. F.: *Ann. Surg.* 93:1152, 1931.

16. Judd, E. S., and Phillips, J. R.: *Ann. Surg.* 98:771, 1933.

17. Heuer, G. J.: *West Virginia M. J.* 26:11, 1930; *Ann. Surg.* 105:758, 1937.

The large, edematous, water-logged gallbladder renders isolation of the cystic duct difficult. Removal of the gallbladder, even from above, entails considerable risk of injury to the deeper ducts. Of all things that one wishes to avoid, that evil result is the least desirable. Partial cholecystectomy will obviate that danger. In the large gangrenous gallbladder which is so friable one can scarcely handle it without rupture and soiling, aspiration and adequate tamponade are essential.

Excision of the diseased or gangrenous wall of the gallbladder leaves the part that is embedded in the fossa of the liver. Having the best circulation on account of its attachment to the liver, it is rarely gangrenous. One need not be afraid of the little part that is left. The surgeon is so imbued with the idea that he must take out every particle of the gallbladder that he is fearful about leaving any part of it.

After the stone or stones and the liquid contents have been removed, the walls of the gallbladder are cut away. Removal of the remnant adherent to the liver is often a bloody procedure and leaves a large raw bleeding surface that is difficult to suture. Multiple drains are usually required. The little piece of gallbladder adherent to the bed of the liver is the patient's protection.

One can remove the mucosa by rubbing it with gauze. Swabbing with phenol will denude it, and the acid is then neutralized with alcohol. Destruction of the mucosa will do away with secretions, and no sinus will result.

The cut edges of the remnant of gallbladder are sewn over a catheter in the cystic duct. Drainage is adequate. It is a most satisfactory way to get out of a difficult situation and avoid adhesions.

DR. DONALD GUTHRIE, Sayre, Pa.: I agree that the operation Dr. Estes has described is the correct one to employ in these desperate situations instead of the more radical operation of cholecystectomy.

The surgeon should use his best judgment in the selection of cases of cholecystitis for operation during the acute phase of the disease, for in spite of all that has been said lately about the need of prompt operation to prevent perforation or gangrene, the tendency is toward conservative treatment. Neither gangrene nor perforation of the gallbladder are feared as much in cases of cholecystitis as in cases of acute appendicitis.

My associates and I have practiced in a measure the plan suggested by Dr. Estes. We remove the mucous membrane and leave the serosa behind, for infection cannot recur in a hollow viscus if the mucous membrane is removed or destroyed.

This procedure is called a compromise cholecystectomy. After the contents of the gallbladder are aspirated and the gallbladder is opened, the organ is split from the fundus to the infundibulum, the margins are widely retracted and the thickened mucous membrane is separated from the cut edges with the handle of the scalpel.

After the mucous membrane is well separated from these edges, it is usually easy to complete its removal with finger dissection. Bleeding vessels are ligated, excess serosa is cut away and the edges are sewed together over a small rubber tube.

It is usually impossible to bring the edges of the liver together after complete removal of a large gallbladder, because the thickened posterior layer of the serosa generally comes away with the gallbladder, and it is often necessary to pack the bed of the liver with gauze to control the bleeding. This is dangerous.

Poor exposure, improper mobilization of the infundibulum and hemorrhage from the cystic artery are frequent causes of injury of the common duct, with the development of a postoperative biliary fistula or a stricture of the common duct.

The plan of Dr. Estes deserves more general adoption, for I believe that the surgeon should be less prone to perform cholecystectomy in the presence of fulminating cholecystitis in an extremely ill patient, and the partial operation has proved to be safe. Furthermore, it is curative, as is so well proved by Dr. Estes' reported cases.

DR. MOSES BEHREND, Philadelphia: I have never been compelled to use this technic. I have used it in cases of chronic cholecystitis simply for teaching purposes, but otherwise I always follow the technic of Max Thorek, of Chicago. I believe that much can be gained by electrocoagulation of the exposed surface of the mucous membrane in place of the use of phenol or actual cautery.

I never use drainage in these cases, but sew the falciform ligament over the fulgurated mucous membrane. In fact, I do not use drainage in any case of cholecystectomy, because I believe that the convalescence is better without it. Formerly I employed drains, but in the last fifteen or twenty years I have discontinued their use entirely.

Dr. Estes opened up an enormous subject when he spoke about operating in cases of acute cholecystitis. I do not believe that he meant one should operate in such cases as an emergency measure. I never performed an emergency operation (and I agree with Dr. Guthrie on this point) in a case of acute cholecystitis or acute empyema of the gallbladder. I wait from eight to ten and even twelve days until the symptoms have subsided. I have never been compelled, therefore, to use the technic described by Dr. Estes.

Even in cases in which there is a hard peritoneal covering over the cystic and common ducts, it is necessary only to make an incision with a sharp knife in the line of direction of the ducts and then to separate the peritoneum with long flat scissors. The ducts can be exposed readily, and an excellent cholecystectomy can be performed.

My mortality is from 1 to 2 per cent. I believe that this is due to the fine exposure of the field of operation and to the fact that I never operate in cases of acute cholecystitis or of acute empyema as an emergency measure.

DR. WILLIAM L. ESTES JR., Bethlehem, Pa.: My deep thanks go to Drs. Haggard, Guthrie and Behrend for their illuminating discussions.

To make it perfectly plain in referring to partial cholecystectomy and its indications, I repeat that this procedure is to be used only in a rather restricted field. It should be used in cases of advanced, acute, suppurative or gangrenous cholecystitis.

I do not consider it an emergency operation. And whereas this is a controversial field, my own feeling is that one should distinguish definitely between an emergency operation and early operation for acute cholecystitis. In other words, a patient with acute suppurative cholecystitis should be properly prepared for operation and not rushed to the operating room; but if he is in a satisfactory condition, he may be operated on early. Partial cholecystectomy is one of the procedures that is applicable in the treatment.

# FRACTURES OF BOTH BONES OF THE LEG

## MANAGEMENT BY USE OF THE DOUBLE STEEL PIN TRACTION IN PLASTER OF PARIS

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AND

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This paper is a summary of the treatment, progress and results of treatment of tibiofibular fractures in 23 consecutive cases managed by the traumatic surgery staff at the Hurley Hospital between Jan. 24, 1935, and Jan. 29, 1937. We have had 7 more cases since the last-named date, but we consider these too recent to be useful in drawing definite conclusions. However, thus far the course has been comparable to that in cases in which we have been able to collect more nearly complete data. In addition, other surgeons on the hospital staff have had 17 cases, which are also not included in this series. Results have been uniformly good as far as can be ascertained.

Enthusiasm for the acceptance of the method of management of tibiofibular fractures by means of the double steel pin came as a result of the work of Dr. R. A. Griswold, of the department of surgery of the Louisville City Hospital and University of Louisville School of Medicine, who described the routine procedure, after-care, results and conclusions in the management of 43 fractures of this nature. The results were considered excellent, and one of us (Curry) decided to adopt the method. While a series of 23 cases may appear rather small, the results obtained seem to justify a report at this time.

In the short period of two years the fundamental principle of traction by steel pins, one through the os calcis and the other through the tibia posterior to the tibial tubercle, has been changed only by the availability at present of specialized apparatus for gaining the approximation of the bone fragments.

In this clinic the indications for the use of the double steel pin method of traction and immobilization in plaster of paris for combined fractures of the tibia and fibula are (1) fracture of both bones of the leg and (2) absence of involvement of any joint.

The treatment used consists, as mentioned, of the insertion of a  $\frac{1}{8}$  inch (0.3 cm.) steel pin through the upper end of the tibia on a level

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From the Department of Traumatic Surgery, Hurley Hospital.

with the anterior tibial tubercle and into the substance of the tibia on a plane approximately  $1\frac{1}{2}$  inches (3.7 cm.) posterior to the anterior plane of the tibial tubercle. The ends of the pin protrude conveniently about  $1\frac{1}{2}$  inches from the surface of the skin on each side. The second, or distal, pin, somewhat shorter, is placed through the body of the os calcis at a point about 1 inch (2.5 cm.) below the external and internal malleoli and slightly posterior to them. The pins are inserted with the patient under either local or general anesthesia. The leg is then lifted, and the ends of the pins are placed in removable

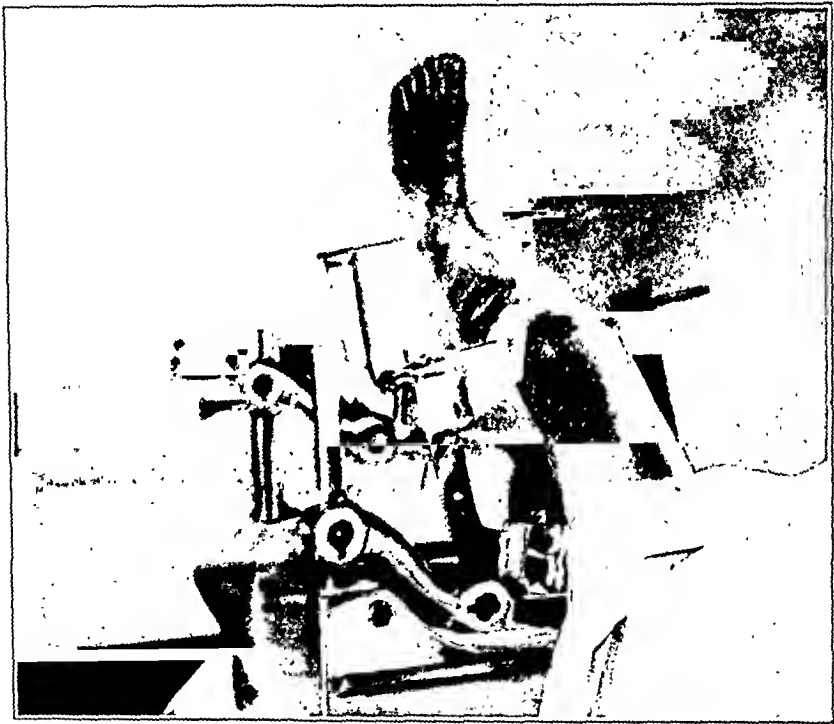


Fig. 1.—Zimmer apparatus used in gaining anatomic apposition of bone fragments. The apparatus is so constructed that changes in length, rotation and height may all be effected by adjustment. A roentgenogram is taken at this stage, or fluoroscopic control is used. A plaster of paris dressing is applied from the toes to the middle of the thigh before the leg, with pins, is removed from the apparatus.

sockets, which are anchored in slits on the proximal and distal portions of the traction apparatus as designed by Zimmer (fig. 1). The clinical alinement of the leg is obtained by rotation of either the upper or the lower fragments and their pin. Traction is exerted by the mechanical attachment for this purpose until the desired length is obtained and until clinical observation, laterally, anteriorly and posteriorly, determines the correct position and length. This is checked by means of a



portable x-ray apparatus; the roentgenogram is developed immediately and is interpreted before the fracture is fixed in plaster of paris. Fluoroscopic control is also recommended, to determine the proper alignment. Plaster of paris is then applied from the base of the toes to the middle third of the thigh, with the foot held at right angles midway



Fig. 2.—A typical tibiofibular fracture, at the time of the patient's admission to the hospital. It fulfils the indication for management with the double steel pin.

between eversion and inversion and with the knee in slight flexion. Pins are incorporated in the plaster of paris, their protruding ends being covered with corks and likewise incorporated in plaster of paris (fig. 3). A walking iron is then applied.

In compound fractures, a débridement of the wound together with a thorough irrigation is done, and the wound is closed. From this point it is treated like a simple fracture. Tetanus antitoxin and gas bacillus antitoxin are given as a part of the routine in all cases of compound

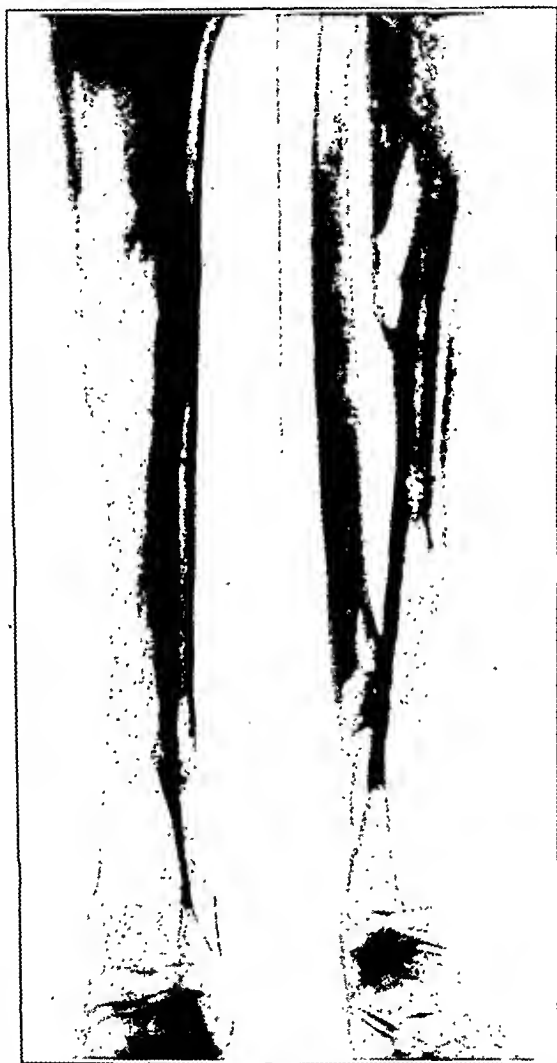


Fig. 3.—The fracture has been reduced by the traction apparatus shown in figure 1. Note that the leg is now in plaster of paris and that the pins remain in place.

fracture. If the fracture is presented late and secondary infection is present, a steel pin is placed through the os calcis for the purpose of traction with weights. When the wound has healed sufficiently the proximal pin is inserted as has been described and a plaster of paris

dressing is applied, incorporating both pins. The patient is kept in bed until his temperature is normal and there are no complications.

As to the etiology of fracture in this series of cases, 10 of the 23 fractures were caused by the patients' having been struck by an automobile; 5 were the result of accidents to persons riding in automobiles; 6 were due to falls, and 2 were the result of farm accidents.

In this series of cases, 10 fractures were compound and the remaining 13 were simple. The roentgenologic diagnosis of these 23 fractures classified 20 as comminuted fractures of the tibia and 3 as spiral fractures of the same bone. In each case the roentgenogram showed an accompanying fracture of the fibula, either at the same level or in the upper third. As to the location of the tibial fractures, 7 occurred at the junction of the upper and the middle third of the shaft, 5 at the junction of the lower and the middle third, 4 in the middle third, 3 in the lower third and 1 in the upper third. One tibia showed fractures at the upper and the middle third, 1 had 2 fractures involving the middle and the lower third, and another had 3 fractures in the upper half of the tibial shaft.

All but 4 of the patients were operated on within a period varying between two and five days after the occurrence of the accident. The operations for these 4 patients were necessarily delayed on account of other major injuries.

One of the outstanding features of this method of treatment is the materially shortened period which elapses before the patient is up and about after the operation (fig. 4). For 19 patients the average time spent in bed after the operation was six days. At the end of this time they were discharged on crutches. The number of days from operation to discharge varied from one to thirteen. The remaining 4 patients had to be kept in bed because of injuries other than the fractures. Many patients were discharged on crutches on the third day after the operation. When the operation took place on the day following admission and the patient was discharged on the third day after the operation, four days of hospitalization had been required, in contradistinction to the months spent in bed by patients given older methods of treatment. No patient whose condition was not complicated by other injuries had a total stay of more than seventeen days in the hospital.

On their discharge from the hospital on crutches, patients are instructed to return to the outpatient department at monthly intervals, unless discomfort or other symptoms bring them in sooner. At these periods check-up roentgenograms are taken to show the progress of the fracture.

In this series of cases the oldest patient was 66 years old and the youngest 7 years old. The fractures in patients from 20 to 40 years old

showed no more rapidity in healing than did those in patients past 40. The fractures in children from 7 to 16 years old, of which there were 3, required approximately one-half the healing time which was required by those in patients more than 20 years old. The average length of time elapsing after the original injury before roentgen evidence of healing was first seen was eighty-one days. The average postoperative period before evidences of healing first appeared through the cast was seventy-



Fig. 4.—This patient was up, on crutches, on the fourth day after the operation, five days after the original injury.

two days. It is to be noted that roentgen evidence of callus is obscured by plaster of paris. The pins were removed when roentgen evidence became positive for maintenance of the position of the bones without the pins. An average healing period of one hundred and twelve days after the operation was found to be satisfactory in this series. A short plaster of paris leg dressing extending from just below the knee to the toes, including a walking iron, was applied at the end of this period.

In the series there were 20 cases of sufficient duration to demonstrate functional union clinically and roentgenologically. The average length of time from the time of injury to the time of functional union was one hundred and fifty days, or one hundred and forty-three days

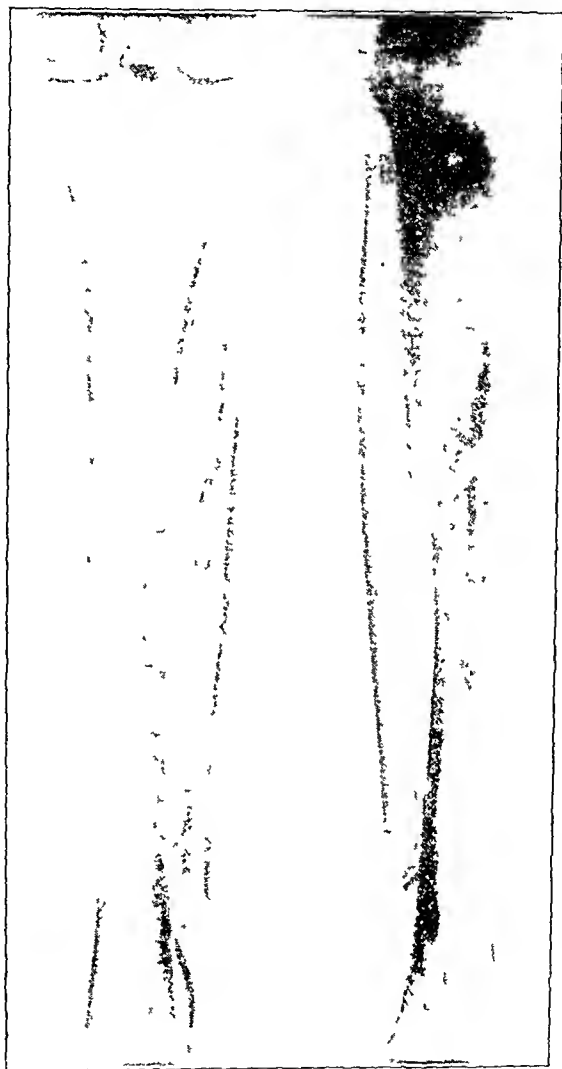


Fig. 5.—Tibiofibular fracture. Note that the pins have been removed and that union is satisfactory one hundred and sixteen days after the original injury. This fracture was kept in a plaster of paris dressing for an additional two months.

after insertion of the pins (fig. 5). However, the patient was kept in a cast and walking iron for an additional two months to insure firm union. The patients were free from all methods of immobilization at the end of an average period of seven months. Compound fractures



Fig. 6.—Final result, seven months after the original injury.

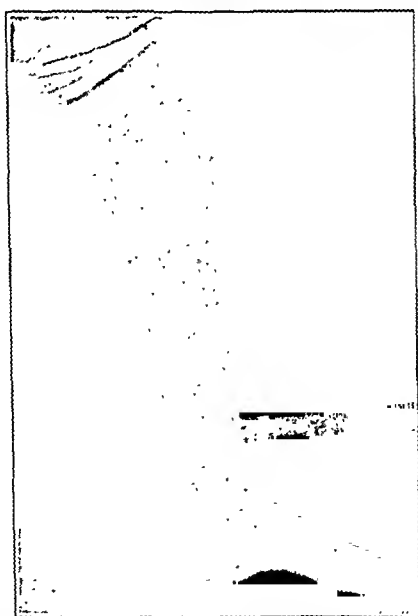


Fig. 7.—Leg after six or seven months' treatment for fracture of both bones. Note the pin scars above and below.

required on an average thirty-six days more to arrive at functional union. In only 1 case did any infection occur about the site of a pin. This was controlled by removal of the pin. There were no sequelae. In the 23 cases in which we have been able to follow the course through at least the first four months after the occurrence of the accident, there has been no instance of nonunion and but 1 instance of delayed union. The fracture in this single case was badly comminuted and compounded and was also infected originally. At present satisfactory union is slowly taking place. Satisfactory alinement and apposition were gained in each case. In no case was there slipping or angulation of the fragments following approximation with pin traction and immobilization by the original cast.

#### CONCLUSIONS

1. Fractures of the leg involving the tibia and the fibula together, not involving a joint, are best treated by the double steel pin traction in plaster of paris.

2. The compounding of a fracture is not an indication for a substitute method or for postponement of the use of this method, although a longer time is necessary for healing.

3. The period of hospitalization is minimal, and the patient is ambulatory early. The economic value of the treatment is obvious.

4. Satisfactory union may be expected within a period varying between seventy and ninety days.

5. The pins may be removed after about three and one-half or four months.

6. Functional union may be expected in five months, but we advise the continued use of the cast and the walking iron for an additional two months.

7. Nonunion has not occurred in this clinic with this type of management.

8. This method maintains anatomic approximation and insures a good functional result.

9. Satisfactory knee and ankle motion are noted after the removal of the cast.

10. The passive congestion associated with dependency of the leg and the irritation of the ends of the bones by the early use of graduated weight bearing are apparently definite stimuli to osteogenesis.

11. Patients are easily managed, happy and contented, and complain of very little pain or discomfort.

# SUPPURATIVE INTRATHORACIC THYROIDITIS

## REPORT OF A CASE

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AND

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Although intrathoracic goiter is relatively frequent, its complication by suppuration is exceedingly rare. In a careful review of the literature, the only case found was one reported by Kalbfleisch<sup>1</sup> in 1920, in which the condition occurred in a young woman following a spontaneous abortion. Gas bacilli were present in the uterine secretions, although no local infection was observed. In the course of her illness, it was noted that a substernal goiter was present. In view of the septic course and local symptoms referable to the goiter, the diagnosis of either a complicating suppuration or a hemorrhage into the thyroid was considered. Operation was performed, and a suppurative intrathoracic goiter due to gas bacilli was found. Drainage was instituted, and recovery followed.

Acute thyroiditis has often been observed. Clute and Lahey<sup>2</sup> described two types: (1) simple thyroiditis, which is more common, usually follows infection of the upper respiratory tract and is generally resolved with conservative management; (2) suppurative thyroiditis, which is rarer and requires surgical intervention. Cochrane and Nowak<sup>3</sup> found acute thyroiditis in 0.5 per cent of all clinical cases of thyroid disease coming under their observation. The infection was usually metastatic, and the common organisms found were the staphylococcus, the streptococcus, the pneumococcus, the typhoid bacillus, the paratyphoid bacillus and the colon bacillus. In 1,985 patients with goiter treated surgically at the Cook County Hospital since 1929, there were only 4 with thyroiditis, an incidence of 0.2 per cent.

Statistics concerning the incidence of substernal or intrathoracic goiter vary considerably in the different clinics, probably because of

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From the Department of Pathology, Dr. R. H. Jaffé, Director, and the Medical Service of Dr. L. C. Gatewood, Cook County Hospital.

1. Kalbfleisch, K. W.: Metastatic Gas Bacillus Infection in a Retro-Sternal Cystic Goiter, *Beitr. z. klin. Chir.* **118**:342-362, 1920.

2. Clute, H. M., and Lahey, F. H.: Thyroiditis, *Ann. Surg.* **95**:493-498, 1932.

3. Cochrane, R. C., and Nowak, S. G.: Acute Thyroiditis, *New England J. Med.* **210**:935-942, 1934.



different modes of classification and terminology. Judd<sup>4</sup> found a substernal projection of the lobes of the thyroid in 50 per cent of patients presenting themselves for an operation on that gland, while the intrathoracic type was noted in less than 5 per cent. Goiter chiefly intrathoracic in location, without any cervical enlargement, was found in less than 1 per cent of the cases. Lahey<sup>5</sup> found no case of intrathoracic goiter in 4,363 cases of exophthalmic goiter or primary hyperthyroidism, but of 5,131 adenomatous goiters, 21 per cent extended into the superior mediastinum and the thorax. Of these goiters, 68 per cent reached nearly to the aortic arch, while 32 per cent extended to or below the arch. Sharer<sup>6</sup> found substernal goiter in 6 per cent of thyroidectomies and cited Higgins as stating that 10 per cent of goiters observed at operation were substernal and from 1 to 2 per cent intrathoracic. In 9,888 consecutive autopsies at the Cook County Hospital since 1929 there were found 1,222 nodular goiters. In this series only 3 true intrathoracic goiters were encountered, an incidence of 0.24 per cent.

Hemorrhage and cystic degeneration or other regressive changes are relatively common in substernal goiter, but suppuration is a rare complication. We are therefore reporting the following case of suppurative intrathoracic thyroiditis, the second case to be described in the literature.

#### REPORT OF CASE

*History.*—M. J., a Negress aged 27, entered the Cook County Hospital on Dec. 24, 1936. She was in such poor condition that a thorough history could not be obtained. However, it was learned that she had been generally well until eight days previously, when she noticed a pain in the right side of her chest, which continued, causing her to be short of breath. Cough was present since the onset, with expectoration, which at times was blood streaked. Chills were thought to have been present.

Physical examination revealed an obese Negress appearing acutely ill. The rectal temperature was 105 F., the pulse rate 154 and the respiratory rate 48. The essential findings were limited to the chest. There were dulness, bronchophony and tubular breathing in the lower lobe of the right lung and a friction rub over the right side of the chest. The heart showed no enlargement, and a systolic murmur was present over the apex. The abdomen was distended, and the liver was slightly enlarged and was tender. The diagnosis was lobar pneumonia of the lower lobe of the right lung.

The patient's condition improved gradually, the temperature falling by lysis. However, moderate lethargy remained, and in her fourth week in the hospital the oral temperature ranged between 99 and 101 F., the pulse rate between 100 and 120 and the respiratory rate between 20 and 30. The pulmonary symptoms were

4. Judd, E. S.: Intrathoracic Goiter, *Internat. Clin.* **1**:149, 1920.

5. Lahey, F. H., and Swinton, N. W.: Intrathoracic Goiter, *Surg., Gynec. & Obst.* **59**:627-637, 1934.

6. Sharer, R. F.: Substernal Thyroid, *Am. J. Surg.* **32**:56-62, 1936.

practically cleared up, and the patient had no complaints. A roentgenogram (fig. 1) showed a small area of infiltration in the lower third of the right lung, a widening of the superior mediastinal shadow and an elevation of the dome of the right side of the diaphragm (Dr. J. P. Bennett). Fluoroscopic examination and further studies were advised, but the patient's condition was too much weakened for these and she died suddenly on Jan. 24, 1937, five weeks after the onset of her illness. Slight icterus was noted.

*Laboratory Findings.*—The white blood count ranged between 22,000 and 24,800. The urine on several examinations was normal. Blood tests and Kalin tests of the spinal fluid gave negative results. The sputum showed no tubercle bacilli.



Fig. 1.—Anterior view showing marked widening of the mediastinum by the substernal nodose goiter.

The final clinical impression was that of lobar pneumonia which had been resolved except for a deep-seated abscess in the lower lobe of the right lung.

*Abstract of Autopsy Report.*—The thyroid gland was enlarged, and from the lower pole of its right lobe there extended a lobular mass through the superior thoracic aperture into the superior and anterior mediastinum, slightly compressing the trachea and the innominate veins (fig. 2). On the right side of the trachea the mass, together with the thyroid, measured 17 by 6 by 7 cm., while on the left side the mass measured 16.5 by 7 by 6 cm. The left lobe of the thyroid could be separated from the mass. It measured 8 by 5 by 5.5 cm. in diameter and contained an oval, pale yellow-gray node 5 by 4 cm. in diameter. The right lobe of the thyroid measured 8 by 3 by 2 cm. When sectioned it appeared light gray-



Fig. 2.—Anterior view showing nodular masses of the right lobe of the thyroid extending into the superior and anterior mediastinum and compressing the trachea. *L*, indicates lungs; *H*, heart.



Fig. 3.—Posterior view showing the nodose goiter in the posterior mediastinum (*M*) and its relation to the lungs (*L*) and the heart (*H*).

brown, was coarsely granular and was rich in colloid material. The mediastinal mass fused with the isthmus portion of the thyroid and was composed of multiple moderately firm spherical and ovoid nodes which varied from 10 to 35 mm. in diameter (fig. 3). The nodes were pale gray-tan and mottled with dark purple-red patches of diameters up to 4 mm. Between the nodes, especially on the right side, there were several cavities from 6 to 11 mm. in diameter filled with a creamy light yellow-gray pus. These cavities were surrounded by firm gray-white tissue.

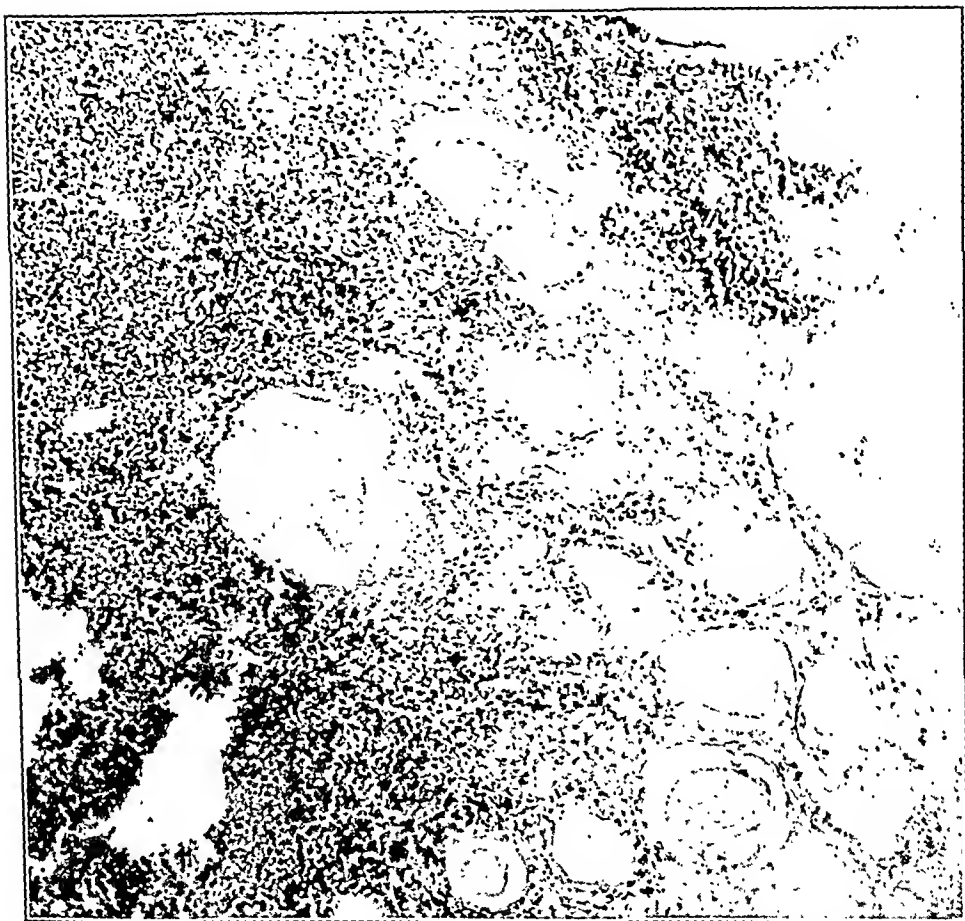


Fig. 4.—Photomicrograph of the wall of the abscess associated with the retrosternal goiter, showing degenerated follicles and the stroma densely infiltrated by polymorphonuclear leukocytes. Magnification,  $\times 150$ .

In the left pleural cavity there were focal fibrous adhesions about the lateral aspect of the upper lobe of the lung, while the right side was partially obliterated by loose fibrous adhesions. Both lungs were moderately distended and were crepitant. The surfaces revealed by section were purple-gray and moist. The pneumonic process had been completely resolved.

There was a slight hypertrophy of the heart, which weighed 360 Gm.

The spleen was enlarged and soft and weighed 190 Gm.

*Microscopic Findings.*—The mediastinal mass consisted of numerous nodes separated by strands of dense connective tissue. The nodes varied in size; the

smaller ones were composed of small and medium-sized follicles filled with a pale-stained, often vacuolated colloid material and lined by a cuboid or low cylindric epithelium. In the larger nodes there were large follicles lined for the most part by a low cuboid epithelium. In places the structure was interrupted by dense accumulations of plasma cells and round cells which infiltrated the septums and extended also into the nodes. Mixed with the plasma cells were a moderate



Fig. 5.—Photomicrograph showing pneumococci in the wall of the abscess cavity. Gram-Weigert stain; magnification,  $\times 1,000$ .

number of iron-filled histiocytes. There were focal deposits of lime salts. In places, recent extravasations of blood were seen. In the periphery of the small nodes, accumulations of pus cells were present, but the most marked suppurative changes were encountered in the large nodes and seemed to select particularly those areas which were the sites of preceding regressive processes (fig. 4). In these areas the follicles were necrotic, the stroma was hyalinized and there were coarse calcium deposits as well as deposits from old and recent hemorrhages.

In the midst of the necrotic tissue were dense accumulations of pus cells with liquefaction of the follicles that were involved.

The left lobe of the thyroid gland was chiefly occupied by nodes composed of large colloid-filled follicles with focal areas of epithelial hyperplasia and proliferation. The stroma contained nets of iron-filled histiocytes. In the right lobe of the thyroid there were nodules made up of small and medium-sized follicles lined by cuboid or low cylindric epithelium.

Gram-Weigert staining of the sections from the substernal mass revealed numerous free lancet-shaped gram-positive diplococci (fig. 5).

*Bacterioscopic Examination.*—In smears taken from the cavities of the substernal portion of the thyroid, numerous lancet-shaped, gram-positive diplococci and clumps of pus cells were found.

*Anatomic Diagnosis.*—The diagnosis was multiple abscesses in a nodose, retrosternal goiter; bilateral nodose goiter; compression of the trachea and the innominate veins by the retrosternal mass; slight hypertrophy of the heart; passive congestion of the lungs; infectious hyperplasia of the spleen, and acute glomerulitis.

#### COMMENT

From the history, autopsic observations and bacteriologic examination of the pus, it may be assumed that the retrosternal thyroiditis succeeded lobar pneumonia which at the time of the autopsy had been completely resolved. The lack of elasticity and the friability of the lower lobe of the right lung were characteristic of the condition of the lung that followed the resorption of a pneumonic exudate. Since the retrosternal goiter was adherent to the mediastinal pleura, one may assume that the infection spread to the thyroid by continuity.

In cases of suppurative thyroiditis the route of infection is usually hematogenous. Such a hematogenous abscess of the thyroid has been observed by us in a case of endocarditis caused by *Streptococcus viridans*.

Clinically, the main symptoms of substernal goiter are produced by the compression of the mediastinal structures, that is, dyspnea, cyanosis of the face and neck, choking spells and dysphagia. When in addition septic manifestations are present, one may suspect a complicating infection of the goiter. In the absence of evidence of compression, roentgenologic examination may furnish the clue as to the focus of infection, namely, the marked widening of the mediastinal shadow.

#### SUMMARY

A case of suppuration in an intrathoracic nodose goiter is presented. The suppuration was apparently secondary to lobar pneumonia which at the time of the patient's death had been completely resolved. The mode of infection of the retrosternal goiter was probably by continuity, since the goiter was adherent to the mediastinal pleura, which in turn was adherent to the lung. Among 1,222 nodose goiters observed at autopsy, 3 intrathoracic goiters were encountered.

# POLYOSTOTIC FIBROUS DYSPLASIA

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My attention was recently drawn by Dr. Henry L. Jaffe, director of the laboratories at the Hospital for Joint Diseases, to a number of cases (4 from this and 4 more from other hospitals from which pathologic material was studied) presenting multiple osseous lesions and having sufficient features in common to differentiate them as a distinct clinical entity. The condition is designated as polyostotic fibrous dysplasia, for reasons to be indicated presently.

## DEFINITION AND NOMENCLATURE

The name "polyostotic fibrous dysplasia" is being used in the Hospital for Joint Diseases to designate a skeletal developmental anomaly affecting several or many bones with predominantly unilateral involvement. The involved bones show filling of their medullary cavities by gritty, grayish white fibrous tissue containing trabeculae of newly formed primitive bone. The condition apparently results from perverted activity of the specific bone-forming mesenchyme. It manifests itself in childhood or early adult life and evolves slowly, pursuing a protracted clinical course characterized by pain, deformity and a tendency to pathologic fracture of the affected bones.

A number of other cases which I regard as instances of the disease have been described in the literature under a bewildering variety of titles, such as, for instance, osteodystrophia fibrosa unilateralis, unilateral polyostotic osteitis fibrosa, unilateral Recklinghausen's disease, osteodystrophia fibrosa cystica generalisata limited to one side of the body, focal osteitis fibrosa, osteitis fibrosa in multiple foci, osteitis fibrosa with formation of hyaline cartilage and osteitis fibrosa disseminata.<sup>1</sup>

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From the Laboratory Division, Hospital for Joint Diseases.

1. A great deal of confusion exists with regard to the nomenclature of skeletal diseases, inherited largely from early investigators. The term "osteitis fibrosa" was employed in the German literature until comparatively recently to include the osseous lesions of hyperparathyroidism, Paget's disease, giant cell tumors, cysts of the bone and localized osteitis fibrosa. The term "fibrous osteodystrophy" has been applied to the same miscellaneous, pathologically unrelated group of osseous diseases, and in fact is still used in the *Index Medicus* synonymously with osteitis fibrosa. The terms nongeneralized fibrous osteodystrophy and unilateral fibrous osteodystrophy, introduced by some authors to obviate the confusion of the

(Footnote continued on next page)

The titles purporting to show the relation of the condition to Recklinghausen's disease of the bone are obviously erroneous, while those emphasizing the unilateral distribution of the affected bones are misleading. The disorder, it is true, shows some tendency to unilaterality. However, in severe forms there is often involvement of the bones on the opposite side and also of the skull and of the vertebral column. Osteitis fibrosa in multiple foci and other similar names qualifying osteitis fibrosa in one way or another are accurate as far as they go but fail to convey an adequate impression of the pathogenesis of the disease. It may be seen that no one of the titles hitherto suggested is altogether satisfactory. I have therefore felt obliged, despite an overburdened nomenclature, to propose the name polyostotic fibrous dysplasia to designate the disease in question.

#### CLINICAL FEATURES

*Incidence According to Age and Sex.*—The youngest patient in my own group was 19 years of age; the oldest, 47. The rest of the patients were women in their early twenties. However, in regard to incidence by age, if one considers cases already reported in the literature, the impression is gained that severe involvement may become clinically manifest in adolescence or even as early as childhood. By the time patients seek treatment, the disease as a rule has already existed for some years, as evidenced by clinical symptoms dating back to the first and second decades of life. In reviewing the histories of my own cases I note that the average age at the onset of symptoms was approximately 10 years. The disease apparently has a distinct tendency to occur in women. The ratio of women to men among the patients in my material and in that of other observers is at least 3 to 1.

*Clinical Manifestations.*—The common clinical signs and symptoms of polyostotic fibrous dysplasia are pathologic fracture, limp, pain and deformity of the affected limb. Pathologic fracture, especially of the femur and occasionally of the humerus, radius or wrist, is perhaps the most frequent symptom. Pain in the hip, also referred to as soreness or stiffness, is another common complaint among those suffering from this disease. Patients may seek treatment also because of shortening of a lower extremity, coxa vara and bowing of the femur, distressing pain in the tibia and occasionally deformity of an upper extremity.

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condition under discussion with generalized osteitis fibrosa cystica, are open to the same objection. It seems to me that the situation would be much clarified if giant cell tumors, simple cysts of the bone of undetermined origin and localized osteitis fibrosa (i. e., fibrosis of the marrow) due to whatever cause were regarded as different entities until more is known of their pathogenesis and the name polyostotic fibrous dysplasia introduced for the clinical entity discussed in this paper.



The long duration of symptoms is an indication of the chronicity of the disease and the slow progression of its osseous lesions. The known duration of symptoms in my series of patients was more than twenty years on the average and in 1 instance as much as thirty-six years.

Precocious menstruation in children suffering from severe forms of the disease has been described by Goldhamer,<sup>2</sup> Borak and Doll<sup>3</sup> and recently by Albright and associates.<sup>4</sup> Goldhamer felt that this manifestation of *pubertas praecox* might in some way be attributed to involvement of the base of the skull. Its significance, however, remains a matter of conjecture.

The presence of hyperpigmentation of certain areas of the skin, apparently due to excessive melanin content, has also been mentioned by Goldhamer and particularly stressed by Albright and his associates as another feature occasionally found in association with the osseous lesions. The precise significance of hyperpigmentation in relation to the osseous lesions is impossible to decide in the present state of medical knowledge. In none of the cases which I have described was excessive pigmentation of the skin noted.

#### DISTRIBUTION OF OSSEOUS LESIONS

The osseous lesions tend to be exclusively or predominantly unilateral, apparently affecting either side without preference. However, bilateral lesions also occur, albeit in a minority of cases. In my material the lesions demonstrable on roentgen examination of the skeleton were entirely unilateral in 3 instances, predominantly unilateral in 2 and bilateral in 1. This is essentially in accord with the composite experience of other observers. The bones of the lower extremity, i. e., the femur and the tibia, according to my experience, are affected much more often than are the humerus and the radius. Combined involvement of lower and upper extremities is not infrequent.

The long bones of the extremities are most often affected and in the following order of frequency: femur, tibia, humerus and radius. Next in order of frequency are the bones of the skull (cranial vault

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2. Goldhamer, K.: *Osteodystrophia fibrosa unilateralis* (kombiniert mit *Pubertas praecox* und mit gleichseitigen osteosklerotischen Veränderungen der Schädelbasis), *Wien. klin. Wchnschr.* **47**:218, 1934; *Fortschr. a. d. Geb. d. Röntgenstrahlen* **49**:456, 1934.

3. Borak, J., and Doll, B.: *Halbseitige Recklinghausensche Knochenkrankheit mit Pubertas praecox*, *Wien. klin. Wchnschr.* **47**:540, 1934.

4. Albright, F.; Butler, A. M.; Hampton, A. O., and Smith, P.: *Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction, with Precocious Puberty in Females*, *New England J. Med.* **216**:727, 1937.

and jaw bones), pelvic bones, ribs and phalanges. Lesions have been noted roentgenographically also in the vertebrae, scapula, clavicle, metacarpals, fibula and other bones. My experience of necropsies on subjects who had had Paget's disease, multiple myeloma, Gaucher's disease and other generalized osseous diseases has indicated that roentgen examination does not begin to reveal the actual extent of involvement of the skeleton. That would probably be just as true for fibrous dysplasia. I realize full well, therefore, that my impressions as to the frequency and extent of the lesions in polyostotic fibrous dysplasia are only as accurate as the roentgen examination of the skeleton is reliable and thorough. In a general way, however, they indicate the relative frequency of at least the conspicuous or well developed osseous lesions.

#### DIAGNOSIS

*Interpretation of Roentgenographic Observations.*—The objective features seen in roentgenograms of bones affected with polyostotic fibrous dysplasia may be summarized as follows: (1) broadening or expansion of the bone; (2) thinning of the cortex; (3) characteristic rarefied and apparently trabeculated appearance, usually erroneously interpreted as indicating "cystic disease," and (4) secondary deformities of affected bones. In the lower extremity, these are principally coxa vara and bowing of the femur or of the tibia. When involvement is severe, the upper end of the femur may be deformed and the neck shortened. Pathologic fracture of the neck of the femur is a frequent development. With severe involvement of the upper extremity, there may be bowing and even spontaneous fracture of the humerus. When the process is well developed, the roentgenogram is usually characteristic, especially if the skeleton as a whole is examined (or at least both femurs, both tibias, the pelvis, the ribs and the skull).

The commonest error in interpreting roentgenograms of the lesions of polyostotic fibrous dysplasia is to construe them as indicating "cystic disease." This explains why in many cases the condition is clinically misdiagnosed as osteitis fibrosa cystica or Recklinghausen's disease of the bone. When the involvement is predominantly unilateral, as it frequently is, the diagnosis of unilateral Recklinghausen's disease has occasionally been made. If attention is focused on a single bone, without roentgen examination of the remainder of the skeleton, an erroneous diagnosis of giant cell tumor, localized cyst of the bone or even enchondroma may be entertained. In point of fact, the involved bones contain no cysts, and biopsy demonstrates beyond a shadow of a doubt that the peculiar appearance of the lesions is due to replacement of the spongy bone and filling of the medullary cavity by fibrous tissue containing spicules of poorly calcified primitive bone. The trabeculated

appearance probably reflects irregularities in the extent of erosion of the inner surface of the cortical bone (fig. 1).

*Chemical Findings in the Blood.*—Estimations of serum calcium were done in the laboratory in 5 cases in which the diagnosis of polyostotic fibrous dysplasia was confirmed by biopsy. The values ranged between 9.8 and 11.0 mg. per hundred cubic centimeters. Values for serum calcium ranging between 11.0 and 11.6 mg. have been noted by other observers also (Borak and Doll,<sup>3</sup> Albright<sup>4</sup> and associates<sup>4</sup> and Freund and Meffert<sup>5</sup>). Apparently, then, the concentration of calcium in the serum may approach the upper limit of the normal range or even be slightly elevated.

Estimations of serum phosphorus show no significant deviation. Nor do any of the other chemical constituents of the blood, with the exception of phosphatase, show any appreciable alteration in their relative concentration.

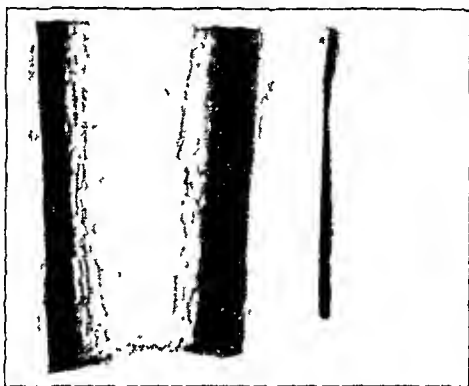


Fig. 1.—Roentgenogram of a portion of a diseased tibia (specimen taken for biopsy in case 2), illustrating the marked thinning of the cortex, the absence of deposition of periosteal bone, the endosteal erosion of the cortex and the filling of the medullary cavity by a homogeneous fibrous tissue containing tiny spicules of bone. Compare with the normal tibia from a woman, on the left.

The phosphatase content, however, was notably increased in 3 of my 4 cases, being 17, 18 and 22 units, respectively, when determined by Bodansky's method (as compared with the normal upper limit for adults of 4 units). Increased serum phosphatase has been noted by other observers also (Albright and associates<sup>4</sup> and Freund and Meffert<sup>5</sup>). The increased values for phosphatase in fibrous dysplasia afford additional support for the hypothesis of Bodansky and Jaffe<sup>6</sup> that the

5. Freund, E., and Meffert, C. B.: On the Different Forms of Non-Generalized Fibrous Osteodystrophy, *Surg., Gynec. & Obst.* 62:541, 1936.

6. Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: III. Serum Phosphatase in Diseases of the Bone; Interpretation and Significance, *Arch. Int. Med.* 54:88 (July) 1934.

activity of the enzyme phosphatase is proportional to the stimulus to the formation of new bone. In this connection, it is interesting to note that in the case in my series in which the value for phosphatase was the lowest (4.1 units) biopsy revealed the least tendency to or capacity for reparative formation of new bone within the fibrous tissue of the lesion, in contradistinction to 2 other cases, in which there was a considerably greater osteogenic tendency, associated with values for phosphatase of 22 and 17 units (Bodansky), respectively. In evaluating the chemical observations of the blood, then, one should remember that the calcium content may be normal or slightly increased and that the proportion of phosphatase is frequently elevated.

#### REPORT OF CASES

In order that the clinicians encountering patients with polyostotic fibrous dysplasia—and the condition is by no means infrequent—may be enabled more readily to recognize it as a clinical entity, the following representative cases with illustrative photomicrographs and roentgenograms are reported.

CASE 1.—The patient was a married woman, 19 years old, who was admitted to the hospital to the service of Dr. Eising on Feb. 24, 1926, complaining of pain in the right hip and a limp. She dated her illness back to an alleged fall at the age of 8, for which she was treated for several months at another hospital. Whether the patient sustained a fracture at that time was not stated. Physical examination revealed limitation of abduction and internal rotation and 1 inch (2.5 cm.) of shortening of the right lower extremity. The clinical laboratory findings were of no particular significance. The tentative clinical diagnosis on admission was traumatic coxa vara and "cystic condition" of the right femur.

Roentgenograms of the right femur disclosed broadening and rarefaction of the upper two thirds. The cortex of the bone was thin but not perforated. There was a focal area of thickening of the cortical bone in the upper third of the femur, which suggested the site of an old healed fracture. The osseous structure had a hazy, ground glass, trabeculated appearance. The upper third of the femur was markedly deformed; the neck was shortened and the position was that of a coxa vara. The lower end of the femur also showed a number of focal rarefied areas. Roentgenograms of the ribs showed expansion of several, notably the ninth and the eleventh, on both sides. Roentgen examination of the bones of the upper extremity, the left femur, the vertebral column and the skull showed no demonstrable osseous defects. Roentgen examination of the femur and tibia nine years later (fig. 2) showed that the osseous lesions had persisted and, if anything, had progressed. There were distinct rarefied and apparently trabeculated lesions not only in the femur but in the upper end of the tibia.

Biopsy of a portion of the ninth right rib was performed for diagnosis. The cortex was extremely thinned, and the medullary cavity was filled with a firm grayish white fibrous tissue. Microscopic examination showed small trabeculae of primitive, poorly calcified new bone irregularly dispersed within the fibrous tissue (fig. 3). Study of the sections in conjunction with the history and the roentgenographic observations indicated that this was a case of polyostotic fibrous dysplasia. The

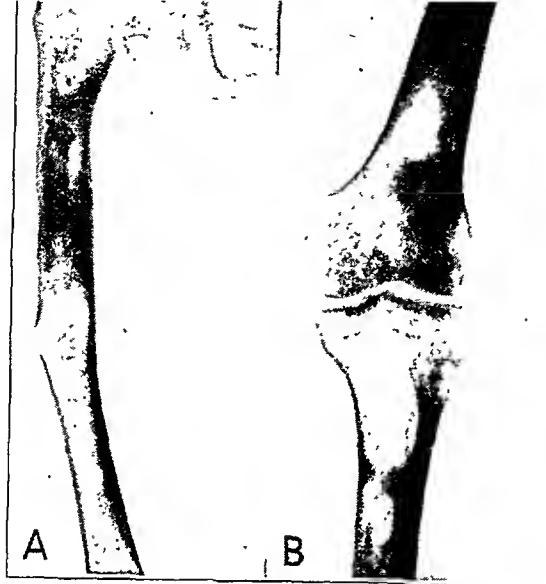


Fig. 2.—*A*, roentgenogram of the right femur in case 1. *B*, roentgenogram of the lower third of the right femur and the upper end of the tibia in case 1.

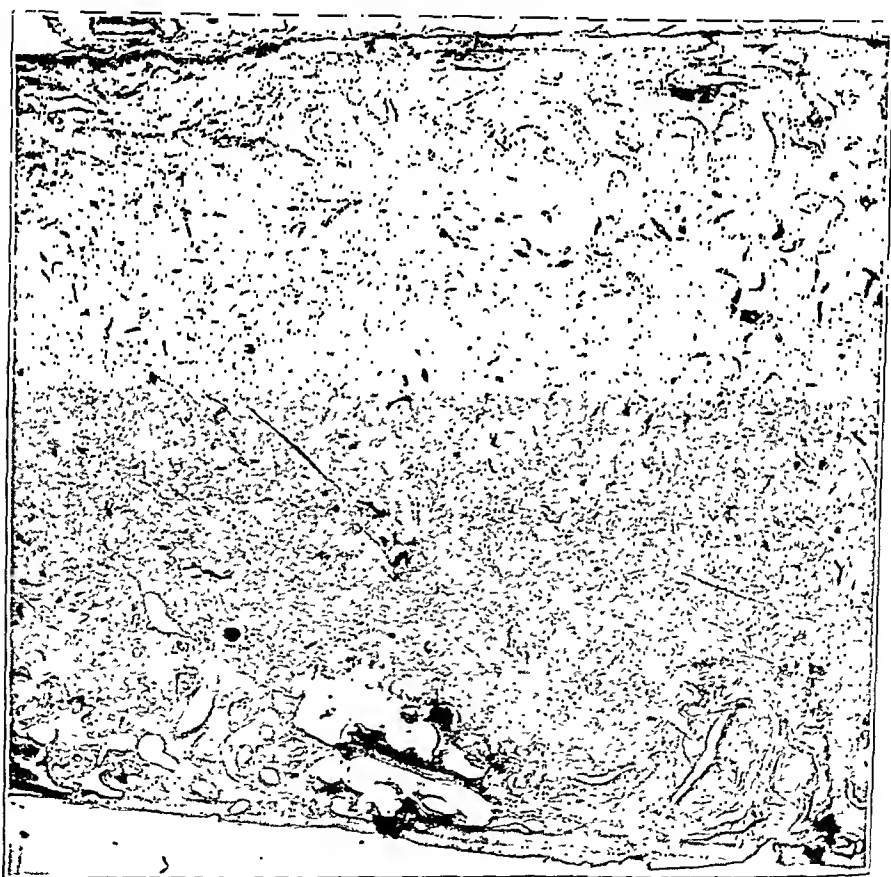


Fig. 3.—Biopsy specimen of a portion of the ninth rib in case 1, cross section, showing the absence of periosteal deposition of new bone, the thinning of the cortex with erosion of the endosteal surface and the medullary cavity filled solidly with fibrous tissue containing small spicules of calcified immature bone ( $\times 15$ ).

surgical wound healed uneventfully, and the patient was treated with ultraviolet rays. For the next several years, however, she complained of persistent soreness in the right thigh, and in 1930 she was operated on at another hospital, where an autogenous tibial bone graft was placed in the right femur (fig. 2 A). Subsequently she was obliged to wear a brace. The follow-up record from the same institution indicates that in 1934 the patient received a series of six roentgen exposures to the region of the parathyroid glands and that in 1936 bilateral exploration of these glands was performed but no enlarged ones were observed.

CASE 2.—The patient, a woman 22 years old, was admitted to the hospital, to the service of Dr. Herman Frauenthal, on July 17, 1935, because of a pathologic fracture of the neck of the right femur. The patient also presented a limp, which she said was first noted at the age of 5. No record of familial incidence was elicited. The past history was irrelevant except for a "traumatic fracture" of the right ankle three years earlier. Physical examination revealed evidences of



Fig. 4.—Roentgenogram of the pelvis and upper portions of the femurs in case 2, showing the involvement of the right femur and ilium, and of the pubis and ischium on both sides.

pathologic fracture of the neck of the femur with upward displacement of the shaft of about  $\frac{3}{4}$  inch (2 cm.). Relative thinning of the right lower extremity was also noted. Chemical findings in the blood were as follows: calcium 10.0 mg., phosphorus 2.0 mg. and phosphatase 22.6 units (Bodansky). Subsequent estimations gave values of 9.8 mg., 2.2 mg. and 18.1 units, respectively. The other data revealed in the laboratory were of no particular significance. The tentative clinical diagnosis on admission was "cystic disease" of the bones. The possibility of Hand-Schüller-Christian disease was considered by some because of the involvement of the skull (fig. 7) and possible slight exophthalmos.

Roentgen examination (figs. 4, 5, 6, 7 and 8) disclosed osseous lesions in the right femur and tibia, in the pubis and ischium on both sides and also in the skull. There was a pathologic fracture through the neck of the right femur with upward displacement of the shaft and the production of a coxa vara. The entire right



Fig. 7.—Roentgenogram of the skull in case 2. The arrows indicate the osseous defects.



Fig. 8.—Roentgenogram of the vertebral column and ribs in case 2, showing lesions in the seventh and eighth ribs.

femur and tibia showed pronounced broadening and rarefaction. The lower end of the femur in particular presented a clublike expansion. The cortex was thinned and slightly irregular. The osseous structure had a mottled, porotic appearance. The contiguous parts of the right ilium, ischium and pubis, as well as the ischium and pubis on the opposite side, were similarly involved. Lesions were noted also in the seventh and eighth ribs and in the eighth dorsal vertebra. A roentgenogram of the skull disclosed two large, ovoid, rarefied osseous defects in the upper parietal and occipital regions. There was also a large blister-like lesion in the occipital bone, which had expanded the outer table of the skull (fig. 8).

Biopsy of the right tibia was performed for diagnosis. The cortex was found to be reduced to a thickness of approximately 1 mm. and the medullar cavity filled with a peculiar type of solid, whitish spongy tissue. Microscopic examination (figs. 9 and 10) showed fibrous tissue in which large trabeculae of immature, poorly calcified new bone had been deposited by osseous metaplasia. The histologic sections, in conjunction with the clinical history and the roentgenographic observations, indicate that this is a case of polyostotic fibrous dysplasia in an active stage. Healing of the wound inflicted in removal of tissue for biopsy was slow but uneventful, and the patient was discharged about two weeks later, walking on crutches. She left New York subsequently, but a personal communication two years later was to the effect that healing of the bone was delayed for more than six months and that pain in the leg had persisted. A local surgeon had suggested exploration of the neck for parathyroid tumor (a common error!) but the patient was advised not to accept this counsel.

CASE 3.—The patient, a woman 20 years of age, was admitted to the hospital on Nov. 3, 1936, to the service of Dr. Kleinberg, complaining of a limp, which had been manifest since she was 10 years old. The patient also complained of stiffness of the left hip and pain on exertion or exposure to cold. Physical examination disclosed a slight limp on the left side, marked posterior curvature of the vertebral column and mild anterior and marked outward bowing of the upper third of the left thigh. Complete restriction of abduction was noted and also marked limitation of inward rotation. There was tenderness in response to pressure over the lesser trochanter. Significant chemical findings in the blood were: calcium 10.4 mg., phosphorus 3.4 mg. and phosphatase 17.1 units (Bodansky). The other laboratory findings, including the value for serum proteins, were within the normal range of variation. The tentative clinical diagnosis on admission was "cystic disease" of the bones. Other possibilities suggested were Ollier's disease and giant cell tumor.

Roentgenograms (figs. 11 and 12) disclosed extensive involvement of the left ilium, femur and tibia. These bones had an expanded, porotic and trabeculated appearance. There was distinct cortical thinning without any perforation. The changes were most pronounced in the ilium and the upper third of the femur but were also evident in the lower third of the femur and in the tibia. Since a specimen of tissue taken for biopsy by means of a punch proved insufficient for diagnosis, it was decided to attempt collapse of the expanded upper end of the femur. The cortex was found to be much thinned out and the medullar cavity filled with a whitish, fibrous, gritty tissue of rubbery consistency. Sections (figs. 13 and 14) showed replacement of the spongy bone and filling of the medullar space by a fibrous tissue made up of spindle cells, in which scattered trabeculae of osteoid and atypically calcified fiber bone had been formed by osseous metaplasia. There was also a number of small focal islands of hyaline cartilage within the





Fig. 2.—*A*, roentgenogram of the right femur in case 1. *B*, roentgenogram of the lower third of the right femur and the upper end of the tibia in case 1.

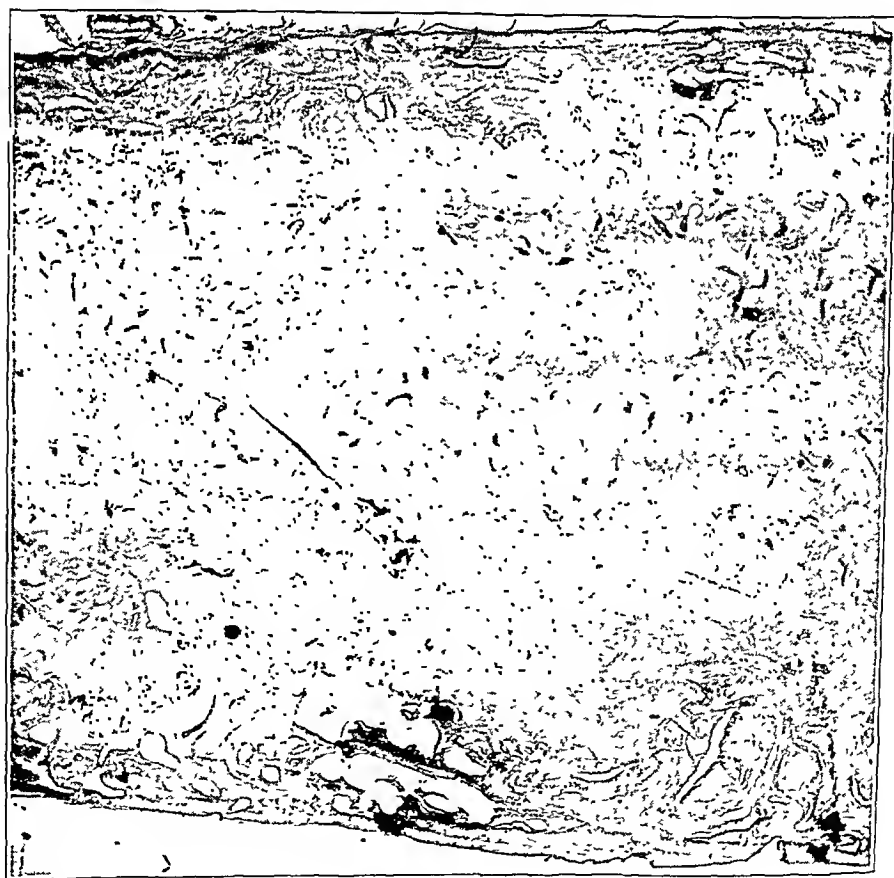


Fig. 3.—Biopsy specimen of a portion of the ninth rib in case 1, cross section, showing the absence of periosteal deposition of new bone, the thinning of the cortex with erosion of the endosteal surface and the medullary cavity filled solidly with fibrous tissue containing small spicules of calcified immature bone ( $\times 15$ ).

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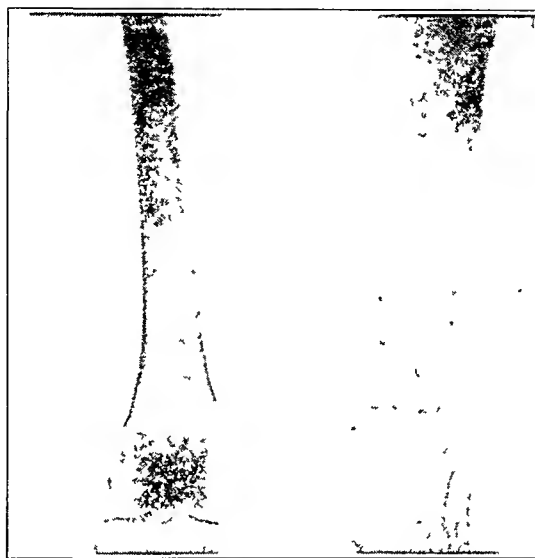


Fig. 5.—Roentgenogram of the lower third of the femurs and upper ends of tibias in case 2. Note the shortening of the affected extremity.

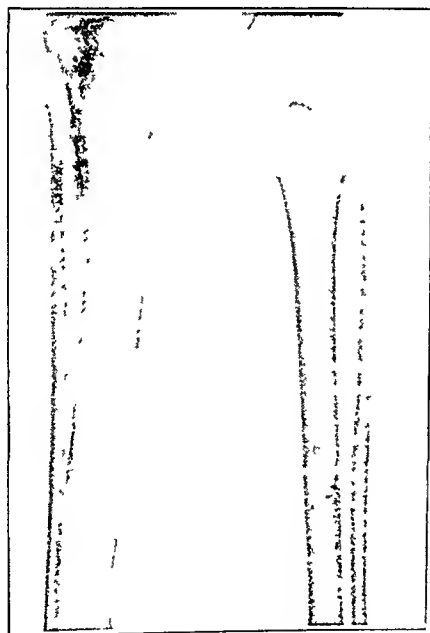


Fig. 6.—Roentgenogram of the tibias in case 2.



Fig. 7.—Roentgenogram of the skull in case 2. The arrows indicate the osseous defects.



Fig. 8.—Roentgenogram of the vertebral column and ribs in case 2, showing lesions in the seventh and eighth ribs.

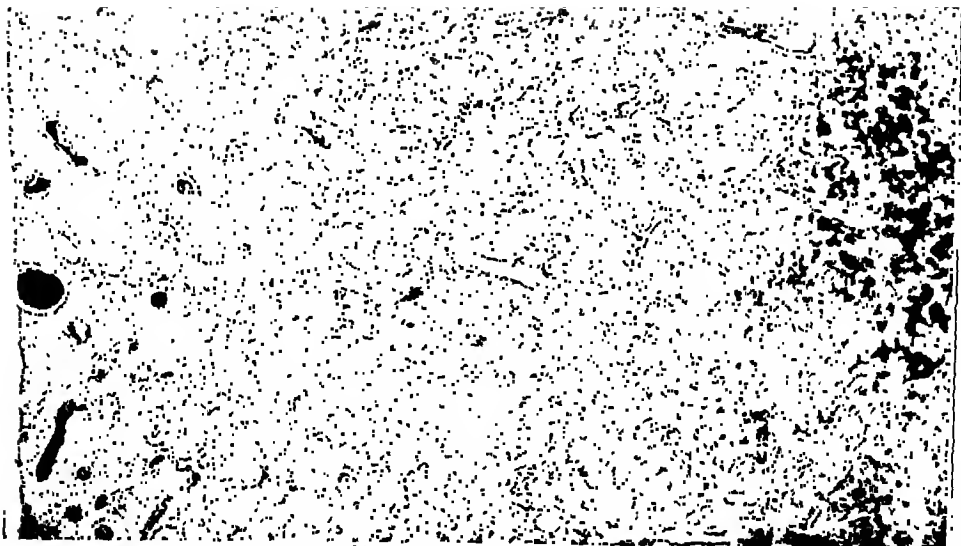


Fig. 9.—Biopsy specimen of the right tibia in case 2. Note the advanced lesion showing considerable deposition of fiber bone in the fibrous matrix and irregular focal calcification ( $\times 15$ ).



Fig. 10.—Biopsy specimen of the right tibia in case 2, cross section, showing absence of periosteal reaction, the thinning of the cortex with endosteal resorption and the replacement of the substantia spongiosa and filling of the medullary cavity by fibrous tissue containing irregular trabeculae of fibrous bone ( $\times 25$ ).

femur and tibia showed pronounced broadening and rarefaction. The lower end of the femur in particular presented a clublike expansion. The cortex was thinned and slightly irregular. The osseous structure had a mottled, porotic appearance. The contiguous parts of the right ilium, ischium and pubis, as well as the ischium and pubis on the opposite side, were similarly involved. Lesions were noted also in the seventh and eighth ribs and in the eighth dorsal vertebra. A roentgenogram of the skull disclosed two large, ovoid, rarefied osseous defects in the upper parietal and occipital regions. There was also a large blister-like lesion in the occipital bone, which had expanded the outer table of the skull (fig. 8).

Biopsy of the right tibia was performed for diagnosis. The cortex was found to be reduced to a thickness of approximately 1 mm. and the medullar cavity filled with a peculiar type of solid, whitish spongy tissue. Microscopic examination (figs. 9 and 10) showed fibrous tissue in which large trabeculae of immature, poorly calcified new bone had been deposited by osseous metaplasia. The histologic sections, in conjunction with the clinical history and the roentgenographic observations, indicate that this is a case of polyostotic fibrous dysplasia in an active stage. Healing of the wound inflicted in removal of tissue for biopsy was slow but uneventful, and the patient was discharged about two weeks later, walking on crutches. She left New York subsequently, but a personal communication two years later was to the effect that healing of the bone was delayed for more than six months and that pain in the leg had persisted. A local surgeon had suggested exploration of the neck for parathyroid tumor (a common error!) but the patient was advised not to accept this counsel.

CASE 3.—The patient, a woman 20 years of age, was admitted to the hospital on Nov. 3, 1936, to the service of Dr. Kleinberg, complaining of a limp, which had been manifest since she was 10 years old. The patient also complained of stiffness of the left hip and pain on exertion or exposure to cold. Physical examination disclosed a slight limp on the left side, marked posterior curvature of the vertebral column and mild anterior and marked outward bowing of the upper third of the left thigh. Complete restriction of abduction was noted and also marked limitation of inward rotation. There was tenderness in response to pressure over the lesser trochanter. Significant chemical findings in the blood were: calcium 10.4 mg., phosphorus 3.4 mg. and phosphatase 17.1 units (Bodansky). The other laboratory findings, including the value for serum proteins, were within the normal range of variation. The tentative clinical diagnosis on admission was "cystic disease" of the bones. Other possibilities suggested were Ollier's disease and giant cell tumor.

Roentgenograms (figs. 11 and 12) disclosed extensive involvement of the left ilium, femur and tibia. These bones had an expanded, porotic and trabeculated appearance. There was distinct cortical thinning without any perforation. The changes were most pronounced in the ilium and the upper third of the femur but were also evident in the lower third of the femur and in the tibia. Since a specimen of tissue taken for biopsy by means of a punch proved insufficient for diagnosis, it was decided to attempt collapse of the expanded upper end of the femur. The cortex was found to be much thinned out and the medullar cavity filled with a whitish, fibrous, gritty tissue of rubbery consistency. Sections (figs. 13 and 14) showed replacement of the spongy bone and filling of the medullar space by a fibrous tissue made up of spindle cells, in which scattered trabeculae of osteoid and atypically calcified fiber bone had been formed by osseous metaplasia. There was also a number of small focal islands of hyaline cartilage within the



Fig. 11.—Roentgenogram of the pelvis and the upper portions of the femurs in case 3.



Fig. 12.—*A*, roentgenogram of the lower end of the left femur in case 3.  
*B*, roentgenogram of the left tibia in case 3.

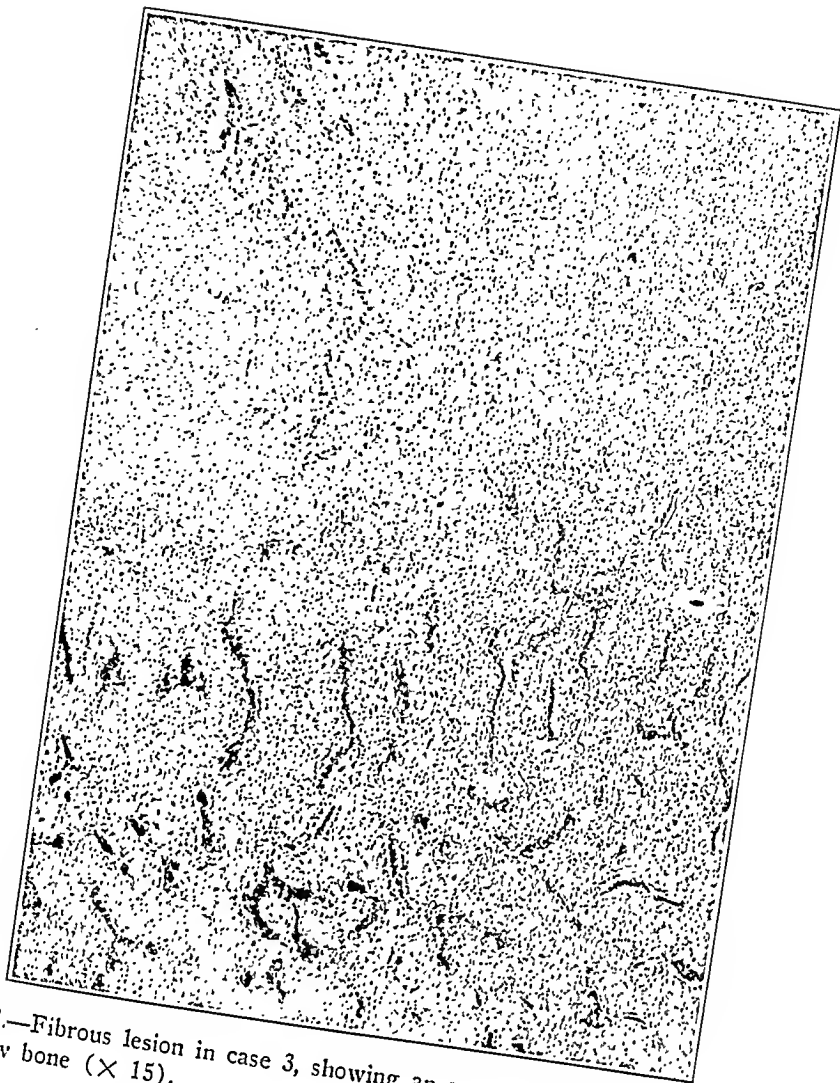


Fig. 13.—Fibrous lesion in case 3, showing an area of relatively sparse deposition of new bone ( $\times 15$ ).

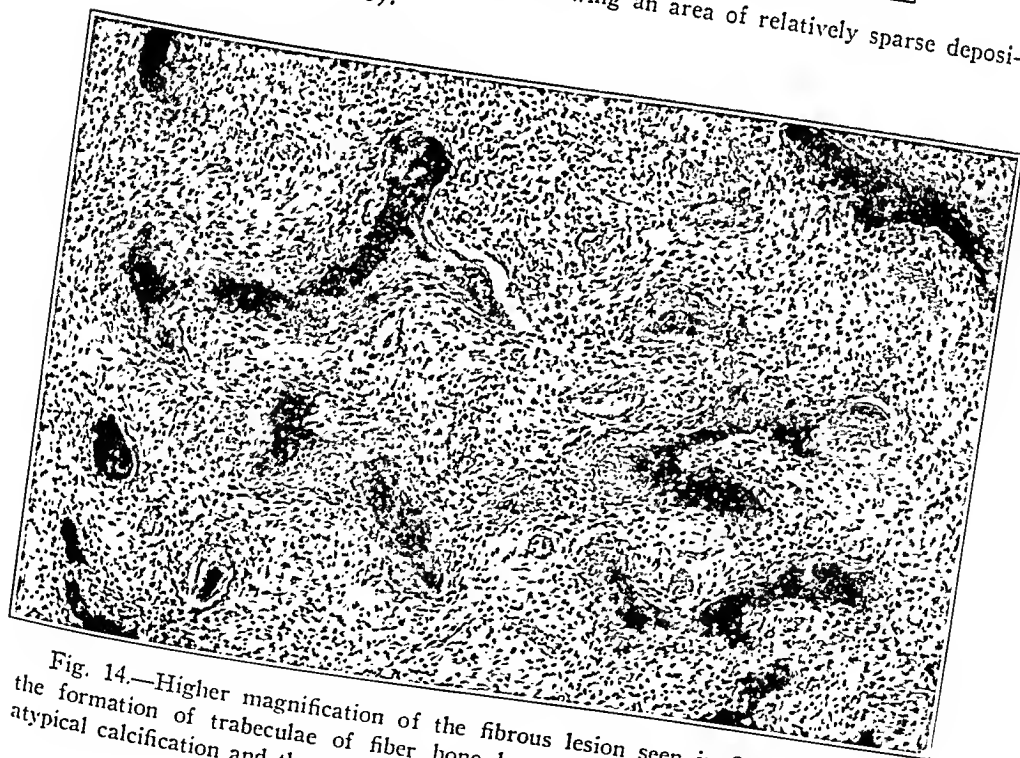


Fig. 14.—Higher magnification of the fibrous lesion seen in figure 13. Note the formation of trabeculae of fiber bone by osseous metaplasia, the irregular atypical calcification and the relatively small number of blood vessels ( $\times 45$ ).



fibrous tissue (fig. 15). Biopsy, in conjunction with the clinical and roentgenographic observations, indicated that this also was a case of polyostotic fibrous dysplasia.

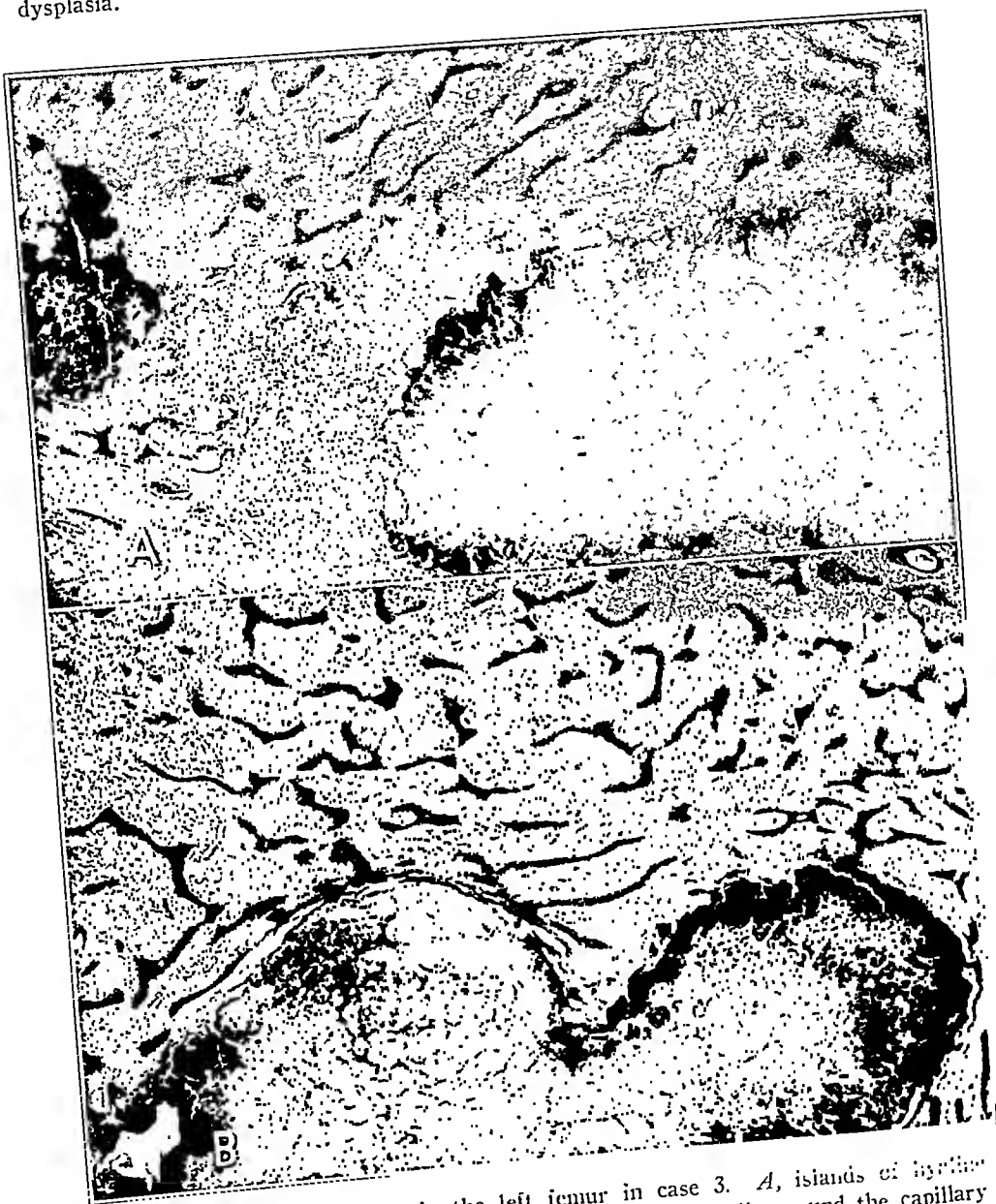


Fig. 15.—Fibrous lesion in the left femur in case 3. *A*, islands of hyaline cartilage undergoing calcification, showing a few giant cells around the capillary extravasation ( $\times 15$ ). *B*, focal area of hyaline cartilage calcified at its periphery ( $\times 15$ ).

Convalescence following the operative procedure was uneventful, and the patient was discharged after three weeks. Several months later she was readmitted because of persistent pain, and a second curettage of the femur was performed. Biopsy

confirmed the previous observations. Chemical analysis of the blood at the time of the second admission gave the following values: calcium 10.9 mg., phosphorus 3.9 mg. and phosphatase 12.4 units (Bodansky). Moderate secondary anemia, which required transfusion, developed after operation. This may be a partial explanation for the lowering of the phosphatase content of the serum. The patient was discharged after several weeks' convalescence.

CASE 4.—The patient, a man aged 47, was admitted to the hospital Oct. 9, 1933, to the service of Dr. Finkelstein, complaining of severe pain in the right tibia. He gave a history of deformity of the right leg dating back to childhood, because of which he was rejected for military service as a youth. He had been referred by the outpatient department for further study, with the suggestion that he might have Paget's disease. Physical examination disclosed marked anterior bowing of the tibia and atrophy of the muscles of the right lower extremity. It was incidentally observed that he presented tremors of the type seen in Parkinson's disease. Chemical findings in the blood were: calcium 10.0 mg., phosphorus 2.7 mg., phosphatase 4.1 units (Bodansky). The other laboratory data were of no particular significance.

Roentgenograms (fig. 16) disclosed pronounced cortical thinning and expansion of the distal third of the shaft of the femur. The osseous structure had a mottled, porotic appearance, with focal areas of diminished density. The most extensive changes were observed in the tibia, which showed medullary expansion, irregular cortical thinning and multiple rarefied osseous defects within the shaft. There was also anterior bowing of the tibia. Roentgen examination of the vertebral column and skull showed no osseous lesions. Biopsy of the right tibia was performed for diagnosis. The cortex was thin and showed evidence of resorption from the medullary side. There was complete absence of periosteal deposition of bone. The medullary cavity was occupied by a gritty, spongy fibrous tissue. Sections (fig. 17) showed small trabeculae of atypically calcified primitive bone irregularly dispersed within the fibrous tissue. Biopsy in conjunction with the clinical and roentgenographic observations indicated that this was a clearcut case of polyostotic fibrous dysplasia. The operative wound healed uneventfully. The severe pain in the tibia was unrelieved, however. In May 1936 the patient was treated in another hospital for erysipelas. Roentgen examination of his skeleton confirmed the presence of the osseous lesions previously noted.

#### PATHOLOGIC PICTURE

There are few comprehensive and well illustrated pathologic descriptions in the literature dealing with the subject. As patients suffering from polyostotic fibrous dysplasia do not ordinarily succumb to the disease, there is no necropsy material available for study. Furthermore, since the osseous lesions are benign, no amputated extremities have been described except in the case reported by Telford,<sup>7</sup> that of a woman 34 years old who requested amputation of a long-deformed lower extremity which showed 5 inches (12.5 cm.) of shortening.

This patient sustained a fracture of the femur at the age of 14, after which swelling of the tibia and progressive shortening of the limb were noted. Examination of the surgical specimen showed the entire femur

7. Telford, E. D.: A Case of Osteitis Fibrosa, with Formation of Hyaline Cartilage, Brit. J. Surg. 18:409, 1931.

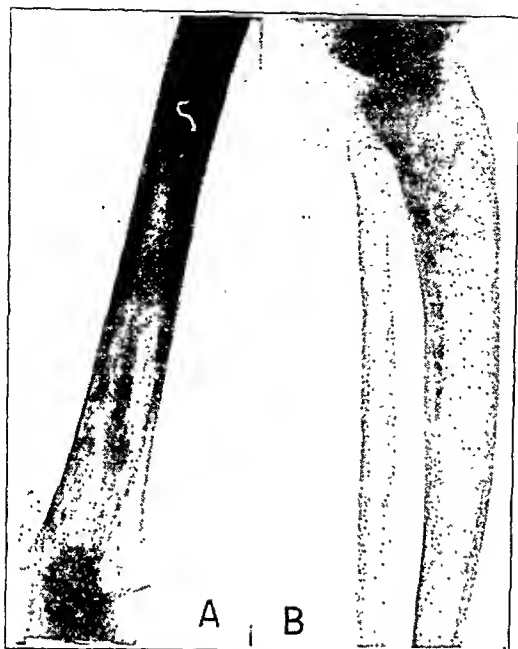


Fig. 16.—*A*, roentgenogram of the lower end of the right femur in case 4.  
*B*, roentgenogram of the right tibia in case 4.

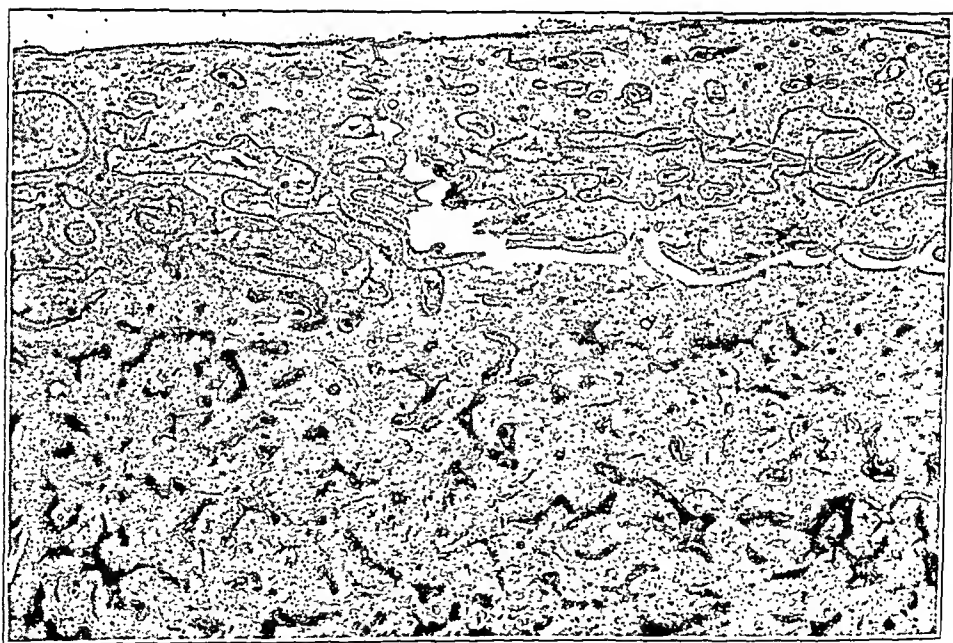


Fig. 17.—Biopsy specimen of the right tibia in case 4, longitudinal section, illustrating the absence of deposition of periosteal bone, the thinning of the cortex with erosion of the endosteal surface by fibrous tissue, which also replaces the substantia spongiosa and fills the medullary cavity and the deposition of trabeculae of primitive bone in the fibrous tissue ( $\times 15$ ).

and tibia, particularly the femur, to be much expanded, deformed and shortened. The cortical bone was reduced to a thin shell, and the medullary cavity was almost completely filled in by a white, fibrous, tough, gritty tissue, containing a few focal areas of hyaline cartilage. Histologic sections, which Professor Telford kindly permitted me to examine, closely resembled those prepared from my own material and indicated that the condition was an advanced stage of polyostotic fibrous dysplasia, limited, roentgenographically at least, to the left lower extremity.

The paucity of satisfactory pathologic material makes it all the more necessary to reconstruct a comprehensive picture of the osseous lesions from the biopsy specimens that are available. My concept of the pathologic nature of the disease is based on a study of 4 adequate specimens taken for biopsy from patients in this hospital, substantiated by gross and microscopic examination of material from 4 other patients submitted to Dr. Henry L. Jaffe from other hospitals. In each instance in which biopsy was performed for diagnosis in the cases in this hospital, both the surgeon and the pathologist concurred in the observation that the cortex was much thinned and that the medullary cavity was filled by fibrous tissue (fig. 1). The latter was described as grayish white or simply whitish; it had a peculiar consistency, variously described as spongy, elastic or rubbery, and was noted to be gritty (because of spicules of calcified new bone). Histologic examination of this fibrous tissue showed definite characteristic features, to be discussed presently. No cysts were encountered in any of the specimens, either on gross or on microscopic examination.

Thinning of the cortical bone, which may eventually be reduced to a thin expanded shell, is due in part to resorption but largely also to erosion of the endosteal surface by the proliferating fibrous tissue. There is, however, no gross or microscopic evidence of periosteal deposition of new bone, except in connection with callus at the site of spontaneous infractions of the cortex. The substantia spongiosa and also the marrow of affected bones are replaced by fibrous tissue. The latter (fig. 14) is composed of spindle cells with oval, pale-staining nuclei and indistinct cytoplasmic outline. The basic connective tissue may in some areas be fairly cellular, while in other areas, on the contrary, there may be a fibroblastic differentiation with a formation of bundles of mature connective tissue, rich in collagen (fig. 13). Special stains for detecting lipid gave negative results. The stroma may be infiltrated by a few small lymphocytes and mononuclear cells.

Dispersed within the fibrous tissue without following any definite pattern, there are small trabeculae of primitive, poorly calcified new bone of variable size and contour. They are apparently developed by osseous metaplasia, without the mediacy of osteoblasts. In the relatively

avascular fibrous areas the trabeculae tend to be sparse in distribution; in the more vascular areas there is usually more extensive deposition of osteoid material and fiber bone (fig. 9). Some of the trabeculae show Howship's lacunas lodging osteoclasts, but on the whole there is comparatively little evidence of osteoclastic resorption. Deposition of calcium within the primitive new bone is variable in extent and distribution. Generally speaking, the bone is calcified poorly and in an imperfect, spotty fashion.

The basic fibrous tissue, on the whole, is relatively avascular, showing only occasional thin-walled vascular spaces. In some areas, however, it may be permeated by a moderate number of capillaries and even occasional small arterioles. Many of the blood vessels are in close proximity to the trabeculae of the bone. The latter are frequently surrounded by slender spaces which because of their endothelium-like lining suggest vascular spaces. Some capillaries appear empty, while others are congested and show small perivascular extravasations of blood. The presence of granules of hemosiderin within phagocytes indicates previous capillary hemorrhages which have been resorbed. In their vicinity one may also encounter small nests of giant cells, resembling osteoclasts. These multinuclear cells are basophilic and may have as many as ten or more nuclei; they are apparently formed by direct transformation and coalescence of the cells of the stroma. While trabeculae, thus suggesting an osteoclastic function, most of them are situated in the soft fibrous tissue. Sporadic islands of hyaline cartilage (fig. 15) may also occur within the fibrous tissue, although this is not constantly observed. The cartilage tends to become calcified, especially at its periphery. The significance of this feature will be discussed presently.

#### PATHOGENESIS

The characteristic pathologic feature of polyostotic fibrous dysplasia appears to be a disturbed function or development of the bone-forming mesenchyme, which results in replacement of the substantia spongiosa and filling of the medullary cavity of affected bones by fibrous tissue in which trabeculae of poorly calcified primitive new bone are developed by osseous metaplasia. The seemingly complex histologic picture becomes much easier to interpret if one predicates the multipotent character of this undifferentiated fibrous tissue, which normally gives rise to the substantia spongiosa and to the myeloid substances or fatty marrow but under pathologic conditions may develop in several anomalous ways. By osseous metaplasia, it gives rise to osteoid material and primitive fiber bone. By cartilaginous metaplasia, it gives rise to sporadic, isolated islands of hyaline cartilage, which tend to become calcified. By fibro-

blastic differentiation, it gives rise to mature collagenous connective tissue. Finally by coalescence of its nuclei, it may give rise to multinuclear cells, indistinguishable from osteoclasts. They apparently represent skeletal phagocytes and are of minor importance so far as pathogenesis is concerned.

The various potentialities of the basic connective tissue may be represented schematically as in figure 18.

The relative extent of the deposition of new bone and the formation of mature connective tissue is variable, depending apparently on the stage and vascularity of the lesion, the severity of the disease and indeterminate factors. Generally speaking, in poorly vascularized areas within the basic fibrous tissue much collagen and little bone are formed; in well vascularized areas deposition of bone proceeds more rapidly. Also, in severe forms with more extensive osseous involvement the basic fibrous tissue shows a tendency to more pronounced osteogenic differentiation. The histologic picture in any given instance may

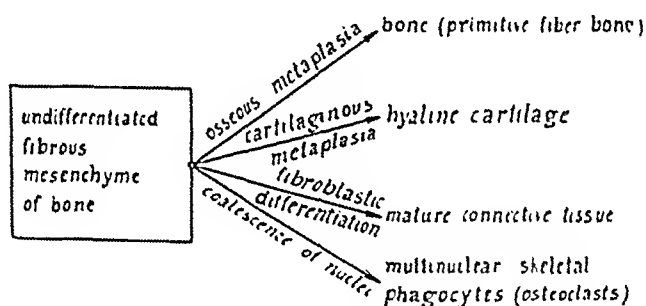


Fig. 18.—Schema showing the various potentialities of basic connective tissue.

run the whole gamut from extensive areas of mature connective tissue with sparse bony trabeculae (fig. 13), on the one hand, to areas composed largely of trabeculae of osteoid material and fiber bone, on the other (fig. 9). The amount of hyaline cartilage deposited is relatively small and indeed may not be detected in limited specimens taken for biopsy. Its development even in small quantity is nevertheless of considerable theoretic interest, in that it suggests a possible relation to another anomaly of skeletal development, skeletal enchondromatosis.

There is no histologic evidence to suggest that the condition is truly neoplastic. Even in the more cellular areas, there are no mitoses and no cellular atypism is noted. Clinically, also, it may be pointed out, no instance of malignant degeneration has been recorded. Nor is there any evidence that the condition is inflammatory in nature. While there may be small foci of lymphocytic infiltration within the fibrous tissue, they are not constantly observed and even when noted are insignificant. Whatever stimulates the continued perverted activity of the undiffer-

entiated fibrous bone-forming mesenchyme, or initiates the disorder, remains of course a matter of conjecture. The clinical histories consistently describing symptoms dating back to early childhood strongly suggest a congenital basis for this curious anomaly of skeletal development. To my knowledge no instance of hereditary transmission of the disease has been recorded.

#### DIFFERENTIAL DIAGNOSIS

The common erroneous clinical diagnoses have for the most part already been indicated, the most frequent being that of hyperparathyroidism. Others include Recklinghausen's disease, unilateral Recklinghausen's disease, osteitis fibrosa cystica and "cystic disease." If only a single bone is examined roentgenographically, a mistaken diagnosis of giant cell tumor or of enchondroma may be made. In an occasional case unilateral involvement may even be mistaken for dyschondroplasia or Ollier's disease (skeletal enchondromatosis with a tendency to attack one side of the body). Traumatic coxa vara and juvenile osteomalacia also are diagnoses that may sometimes be made before further investigation reveals the real nature of the lesion. Paget's disease and malignant disease of the bone are two other possibilities which may sometimes be considered, but which can easily be dismissed after roentgenographic and pathologic examination.

*Hyperparathyroidism (Osteitis Fibrosa Cystica, Recklinghausen's Disease of the Bone).*—Hunter and Turnbull<sup>8</sup> (1931), who described in connection with their discussion of hyperparathyroidism 3 instances of the disease under the title "osteitis fibrosa in multiple foci," realized that the condition was not Recklinghausen's disease and warned against unnecessary exploration. Jaffe,<sup>9</sup> likewise, considering the condition in connection with the differential diagnosis of hyperparathyroidism, emphasized that it has frequently been misinterpreted as Recklinghausen's or Paget's disease. He also recognized that it constitutes a still unidentified entity, having a possible congenital basis. Nevertheless, even at present, polyostotic fibrous dysplasia is frequently confused with hyperparathyroidism. This difficulty arises principally from the fact that the osseous lesions in the two diseases may roentgenographically have a striking resemblance, which is readily misleading to those who are as yet unfamiliar with the clinical picture of polyostotic fibrous dysplasia. In at least 6 instances, as reported in the literature, patients

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8. Hunter, D., and Turnbull, H. M.: Hyperparathyroidism: Generalized Osteitis Fibrosa, *Brit. J. Surg.* **19**:203, 1931.

9. Jaffe, H. L.: Hyperparathyroidism (Recklinghausen's Disease of Bone), *Arch. Path.* **16**:63 (July): 236 (Aug.) 1933.

were subjected to exploration for parathyroid adenoma because of the mistaken clinical diagnosis of hyperparathyroidism. In each instance the parathyroid glands were found to be normal in size and appearance. Two additional patients were needlessly subjected to roentgen irradiation of the neck under the same erroneous premise.

Actually, however, in cases of well developed polyostotic fibrous dysplasia, the diagnosis is evident if one keeps the possibility in mind. The clinical history and roentgenographic observations, as previously indicated, are usually rather characteristic. Other differential features which help to rule out hyperparathyroidism are the high incidence of fibrous dysplasia in childhood and adolescence, its predominantly unilateral distribution and the fact that the unaffected bones appear normal roentgenographically, without evidence of porosis. Furthermore, the calcium in the serum in many cases of fibrous dysplasia is within the normal range. Moreover, studies in the balance of calcium, as reported by Albright and associates,<sup>4</sup> show no appreciable loss of calcium by excretion.

In some few equivocal cases, in which the osseous lesions are not roentgenographically definitive and in which the amounts of calcium and phosphatase in the serum are somewhat elevated (as they may be in polyostotic fibrous dysplasia), it would seem wise to excise a bit of one of the affected bones for biopsy before attempting exploration of the neck for parathyroid adenoma. With reference to the concept of unilateral Recklinghausen's disease proposed by some authors (Goldhamer<sup>2</sup> and Borak and Doll<sup>3</sup>) to explain instances of polyostotic fibrous dysplasia, one need simply reiterate that the disease is in fact neither exclusively unilateral nor due to hyperparathyroidism. Moreover, even the theory is unsound, since it is manifestly illogical to expect that a disease resulting from hyperfunction of endocrine glands would affect the bones of only one side of the body.

*Skeletal Enchondromatosis (Dyschondroplasia or Ollier's Disease).*  
—One of the less frequent errors in clinical diagnosis is to confuse polyostotic fibrous dysplasia with skeletal enchondromatosis. This arises from the fact that in both conditions the osseous involvement may sometimes be predominantly unilateral. However, the clinical and roentgenographic picture otherwise readily suffices to distinguish the two diseases. Other considerations which help to rule out skeletal enchondromatosis are the onset of symptoms in childhood or adolescence rather than early infancy, the absence of macroscopic enchondromas in the metacarpal, metatarsal and phalangeal bones and the less pronounced shortening of affected extremities in polyostotic fibrous dysplasia. Furthermore, a biopsy will definitely establish the diagnosis. While occasional small islands of hyaline cartilage may be found in polyostotic



fibrous dysplasia, the basic histologic picture is one of fibrous tissue in which small trabeculae of immature fiber bone are deposited.

*Hand-Schüller-Christian Disease.*—Young subjects are particularly susceptible also to Hand-Schüller-Christian disease, and it too may cause punched-out rarefied lesions, visible roentgenographically in the skull and other bones. Even pathologic fracture of the femur may be simulated. The resemblance is superficial, however, so that xanthomatosis of the bones due to cholesterol can be ruled out usually on clinical grounds, because of the absence of the Christian syndrome, and if necessary by biopsy.

#### POSSIBLE RELATION TO LOCALIZED LESIONS APPARENTLY AFFECTING ONE BONE

The relation of localized fibrous osseous lesions apparently affecting only one bone to polyostotic fibrous dysplasia is a problem that cannot be definitely decided at present. Freund and Meffert<sup>5</sup> have described two such localized lesions apparently limited to the femur, which roentgenographically and also on biopsy closely resemble the polyostotic form of the disease. Recently I examined sections, sent to Dr. Jaffe, of a biopsy specimen obtained from a girl, aged 14, who presented a solid expanded lesion of the maxilla of the jaw. The condition was diagnosed clinically as central osteoma. The histologic appearance of the lesion, however, was indistinguishable from that seen in polyostotic fibrous dysplasia. Although there were no symptoms referable to other bones, roentgen examination of the skeleton, especially of the long bones, was recommended. Several similar cases have been described by Phemister and Grimson<sup>10</sup> as instances of fibrous osteoma of the jaw.

I have seen also a patient with a localized, expanded, rarefied lesion of the clavicle, diagnosed clinically as giant cell tumor or enchondroma. Biopsy showed the affected portion of the clavicle to be filled with whitish fibrous tissue such as is seen in polyostotic fibrous dysplasia. Roentgen examination of the other bones disclosed only a few suggestive lesions in the ribs.

Localized fibrous lesions of the type described may be regarded as representing a limited form of polyostotic fibrous dysplasia. Since the evolution of the disease is relatively slow, it would not be at all surprising to observe that other osseous defects subsequently develop in these patients. Another possibility is that there *are* multiple osseous lesions in these instances but that some of them are not sufficiently well developed to be visualized roentgenographically.

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10. Phemister, D. B., and Grimson, K. S.: Fibrous Osteoma of the Jaws, *Ann. Surg.* **105**:564, 1937.

# PROGNOSIS AND TREATMENT

So far as is known, polyostotic fibrous dysplasia is a chronic, slowly developing disease, which becomes manifest generally in childhood and persists throughout adult life. Indeed, I have observed two representative cases, with diagnosis proved by biopsy, in patients in the fifth decade of life. The condition is not self limited in the sense that affected bones are ever restored to their normal structure. Study of the available material for biopsy has indicated, however, that in older patients there may be demonstrably less evidence of activity of the lesions and that a sort of static equilibrium may eventually be established. There is of course no specific medical therapy available.

Elective surgical procedures employing curettage and bone grafts for the purpose of strengthening extensively involved, attenuated and expanded bones do not seem altogether warranted, since the same fibrous tissue fills in again. Furthermore, operative wounds may heal relatively slowly, and pain may be aggravated by surgical intervention rather than alleviated. In one of my patients, there were delayed healing and persistent pain two years after partial ostectomy of the tibia. In other instances, six months to a year was required for solid bony union. Surgical intervention, then, should be limited to the treatment of spontaneous fractures and to osteotomy in selected cases, for the correction of severe bowing of the long bones. Because of the pronounced tendency to spontaneous fracture in extensively involved bones, principally in the neck of the femur and occasionally in the humerus, patients should be cautioned to avoid minor traumas and to refrain from unduly strenuous exercise or other activity which might induce a fracture. It would appear worth while to try roentgen irradiation in small or moderate dosage, to ascertain empirically whether it has any beneficial effect. However, it is important to bear in mind that large doses may lead to radiation necrosis of the thinned cortical bone, with resulting pathologic fracture. I know of such an instance.

## SUMMARY

Polyostotic fibrous dysplasia, as I conceive it, is a skeletal developmental anomaly, usually affecting several or many bones, with predominantly unilateral involvement. Lesions on the opposite side of the body do occur, however. The disease is by no means uncommon and is observed most often in children and young adults. The available data indicate, further, a definite tendency to occur in women. The cause is unknown; however, symptoms consistently dating back to early childhood suggest that the disorder is congenital, but evolves slowly. Unlike some of the other diseases resulting from anomalous skeletal develop-

ment, e. g., multiple exostosis and achondroplasia, no familial incidence or hereditary tendency has thus far been noted.

The long bones of the lower extremity (femur and tibia) are most frequently affected, but those of the upper extremity (humerus and radius) and also the skull, ribs, pelvis, phalanges and other bones may be involved. Epiphysoid bones (carpals and tarsals) and bones pre-formed in membrane as well as in cartilage may be affected. The epiphyses of affected bones as well as their metaphysial and diaphysial regions may be involved. The condition runs a slow, progressive clinical course over a period of many years, even decades, with a tendency to spontaneous fracture and deformity of affected bones. The characteristic pathologic feature appears to be a disturbed function or development of the bone-forming mesenchyme, resulting in the filling of the medullary cavity of affected bones by fibrous tissue, in which spicules of poorly calcified primitive fiber bone are developed by osseous metaplasia. Some areas, however, may show a predominantly collagenous differentiation with comparatively little deposition of new bone. Furthermore, small islands of hyaline cartilage (remote from the epiphysial plate) may also be formed by chondrogenic metaplasia.

The aforementioned changes result in prominent widening of affected bones, marked thinning of their cortices and replacement of the cancellous bone and bone marrow by a fibrous, whitish, gritty, solid tissue. The bones on roentgen examination cast a shadow of diminished density, suggesting a rarefied or porotic trabeculated lesion, replacing bone and usually interpreted as indicating cystic disease. Thus, the condition with which polyostotic fibrous dysplasia is most often confused is *ostitis fibrosa cystica* (Recklinghausen's disease of bone). The not infrequent observation of increased values for calcium and phosphatase in the serum in cases of fibrous dysplasia affords another pitfall, suggesting the erroneous diagnosis of hyperparathyroidism. Indeed many patients suffering from polyostotic fibrous dysplasia are subjected to exploration of the neck for parathyroid adenoma only to have the surgeon find normal parathyroid glands. The differentiation from other skeletal diseases has been discussed.

# ARCHIVES OF SURGERY

VOLUME 36

JUNE 1938

NUMBER 6

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## TUMORS OF THE SPINE

WITH A CONSIDERATION OF EWING'S SARCOMA

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BALTIMORE

Originally it was intended to present in this study a classification of primary tumors of the spinal column and of tumors metastasizing to the spine or invading it from contiguous structures. However, it soon becomes evident that Ewing's sarcoma of bone in the region of the spinal column presents certain features of special interest. The relation of this condition to tumors of neuroblastic origin has been given detailed consideration.

This study has been limited, for clinical reasons, to tumors affecting bone. With patients who have pain in the back or symptoms of pressure on the spinal cord, or both, the roentgen study is usually the deciding factor in diagnosis before operative procedures are undertaken. While excellent articles dealing with the roentgenologic diagnosis of spinal tumors have appeared, most of these have dealt with a single type of tumor. For this reason a composite picture with special reference to the incidence of spinal tumors and to their pathology is presented, based on a larger series of cases.

The material used is from the records of the surgical pathologic laboratory and from the neurosurgical department of the Johns Hopkins Hospital. Because of the manner in which this material was collected, the incidence of the various tumors has not been determined with absolute exactness, but for practical purposes the percentages found should be significant.

In all, there were 291 tumors in this series. All of them affected bone or were demonstrable roentgenologically. They included metastatic carcinoma, primary tumors of the spinal column (mainly of osseous origin), glial tumors and tumors of the neural sheath of the spinal cord, tumors of generalized distribution (such as multiple myeloma), tumors of the sympathetic nervous system and tumors of teratologic origin. These types of tumor are mentioned in the order of their frequency.

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## METASTATIC CARCINOMA

Metastatic carcinoma was by far the most frequent neoplastic lesion of this series. Of 291 spinal tumors, 172 (59.1 per cent) were metastatic carcinomas. Schlesinger<sup>1</sup> and Frazier,<sup>2</sup> the former obtaining his data from autopsies and the latter taking his from operations, pointed out the marked frequency of metastatic lesions of the spine. In adults such lesions must be considered in the differential diagnosis of any tumor affecting the vertebral column. Table 1 lists the sites of origin of the 172 tumors.

Schlesinger in 13,500 autopsies found 59 metastatic carcinomas of the spine and listed their sites of origin (table 2).

These two tables present notable differences. Prostatic carcinoma is probably not as frequent as is indicated by the figures in table 1, since in obtaining these figures all the patients with prostatic cancer in the Brady Urological Institute of the Johns Hopkins Hospital were

TABLE 1.—*Site of Origin of Metastatic Carcinomas of the Spine Observed in the Laboratory of Surgical Pathology*

Site of Origin	Number of Cases
Prostate.....	86
Breast.....	60
".....	14
".....	5
Stomach.....	4
Thyroid.....	1
Lung.....	1
Nasopharynx.....	1
Total.....	172

examined. It will also be noted that cancer of the female genital tract is not listed in table 1. Behney<sup>3</sup> has shown that of 55 carcinomas of the uterine cervix which metastasized, 5 had metastases to the lower lumbar vertebrae. This should make the condition a frequent source of metastasis to the spine. These and other discrepancies in the two tables are explained by the different methods by which the material was collected. Table 2 undoubtedly shows more nearly the correct incidence.

Carcinoma of the breast may be considered the most frequent cause of metastases to the vertebrae. In a series of 100 carcinomas of the breast metastasizing to bone (Geschickter and Copeland<sup>4</sup>) 60 of the

1. Schlesinger, H.: Beiträge zur Klinik der Rückenmarks- und Wirbeltumoren, Jena, G. Fischer, 1898.

2. Frazier, C. H., and Allen, A. R.: Surgery of the Spine and Spinal Cord, New York, D. Appleton and Company, 1918.

3. Behney, C. A.: Advanced Carcinoma of the Cervix, with a Report of One Hundred and Sixty-Six Necropsies, Am. J. Obst. & Gynec. 26:608, 1933.

4. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, ed. 2, New York, American Journal of Cancer, 1936.

tumors were found to be in the spine. The condition has no predilection for any particular part of the spine and is usually an osteolytic process, though osteosclerosis may be produced. The site of origin is sometimes not easily detected. The tumor may be small and may pass unnoticed, or, as is so often the case, the carcinomatous breast may have been amputated years before. In case 1 an interval of fourteen years elapsed between the amputation of the breast and the appearance of metastasis in the spine.

CASE 1.—A white woman aged 58 had a breast amputated for carcinoma in 1920. In September 1933 she began to complain of pain in the back. Roentgen examination in April 1934 revealed partial destruction of the body and the left transverse process of the fourth lumbar vertebra. The osteolytic process progressed, and in February 1935 treatment by roentgen irradiation was begun. A roentgenogram taken in June 1935 showed osteosclerosis in the region of the fourth lumbar vertebra (fig. 1). The patient died in September, and autopsy revealed

TABLE 2.—*Site of Origin of Metastatic Carcinomas of the Spine in Schlesinger's<sup>1</sup> Series*

Site of Origin	Number of Cases	Site of Origin	Number of Cases
Mammary gland.....	10	Bladder.....	1
Testis.....	9	Ovary.....	1
Uterus.....	9	Sigmoid flexure.....	1
Bronchus.....	6	Rectum.....	1
Stomach.....	5	Kidney.....	1
Prostate.....	4	Adrenals.....	1
.....	3	Larynx.....	1
.....	2	Pancreas.....	1
.....	2	Origin not given.....	1
Total.....			59

metastatic carcinoma, histologically similar to the primary growth, in the fourth lumbar vertebra, the liver and the lung.

Carcinoma of the prostate is more characteristic in its metastasis to bone. In 134 cases it involved the spine in 86 and showed a marked tendency to appear in the sacral and the lumbar vertebrae. It produces a lesion which is predominantly osteosclerotic. In case 2 the patient lived three and one-half years after the recognition of the metastasis.

CASE 2.—An elderly white man complained of symptoms of urinary obstruction present for six months and of lumbago present for two months. Roentgen examination in August 1927 showed osteosclerosis of the body of the second lumbar vertebra (fig. 2). A conservative operation for prostatic cancer was done at this time and was followed by roentgen irradiation of the prostatic area and of the spine. Roentgen examination in November 1930 revealed generalized osteosclerosis of the spine. The patient died early in 1931.

Case 3 demonstrates that the primary focus of the cancer may remain undiscovered until postmortem examination. It was a case of renal carcinoma.



Fig. 1 (case 1).—Metastatic carcinoma of the breast in the fourth lumbar vertebra. The roentgenogram shows osteosclerosis following irradiation. (Case of Dr. Warner Watkins, Phoenix, Ariz.)



Fig. 2 (case 2).—Metastatic lesion of carcinoma of the prostate in the spine. The roentgenogram shows sclerosis of the body of the second lumbar vertebra.

CASE 3.—A white man aged 66 complained of pain in the back as his only symptom. Roentgen examination in February 1925 showed a destructive lesion in the body of the second lumbar vertebra producing partial collapse. A soft tissue mass was also visible to the left of the spine. Death occurred in May, and post-mortem examination revealed a carcinoma of the left kidney with metastasis to the second lumbar vertebra and to the ribs. Figure 3 shows the lesion found at autopsy. The uniform collapse of the body, the "accordion effect" described by Fray,<sup>5</sup> is well shown. The intervertebral disk was well preserved. The metastatic lesions of renal carcinoma are usually osteolytic and tend to occur in the dorso-lumbar region when the spine is affected.

In the diagnosis of metastatic carcinoma of the spine it must be remembered that in most cases the lesions are multiple. A solitary

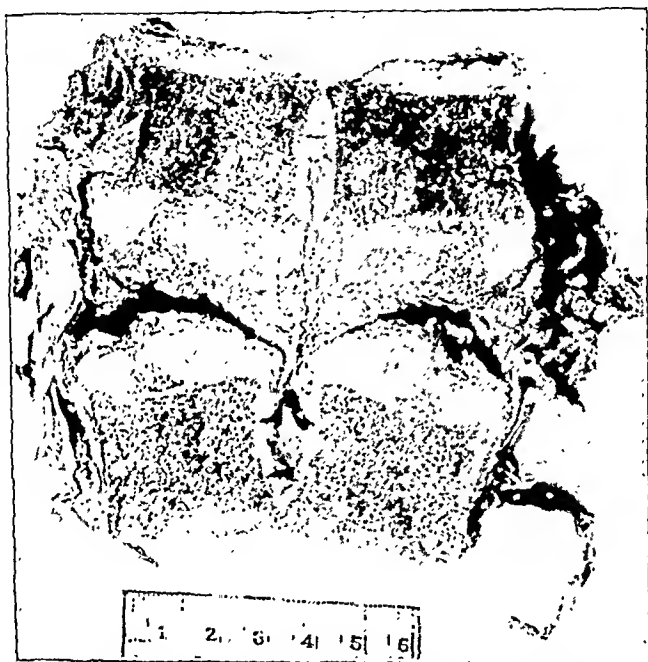


Fig. 3 (case 3).—Hemisection of metastatic renal carcinoma in the spine. The body of the second lumbar vertebra is entirely destroyed. The intervertebral disks are well preserved.

lesion occurred in only 25 per cent of cancers of the breast metastasizing to bone. Consequently, roentgen examination of the entire skeleton is often necessary. A careful search for a primary focus must be made, the most important sites being the breast, the prostate, the cervix, the thyroid, the esophagus and the lung. As may be seen in table 1, a relatively large number of carcinomas of undetermined origin are

5. Fray, W. W.: The Differential Diagnosis Between Infection and Malignancy in Cases of Dorsal Paravertebral Mass, *Am. J. Roentgenol.* **35**:591, 1936.



encountered. As regards the roentgenologic picture, the tendency of metastatic carcinoma of the prostate to cause osteosclerosis is the only consistently recognizable feature. Roentgen irradiation of the affected area, rest and sometimes operative relief of compression of the spinal cord are indicated. The affected part of the spine should be protected by immobilization or by hyperextension. Life is often greatly prolonged by roentgen therapy, and pain may be controlled.

#### TUMORS OF GENERALIZED DISTRIBUTION

It is well to consider generalized neoplastic diseases in conjunction with metastatic carcinoma, since multiple myeloma, the most important representative of this group, as regards the spine, is easily confused with metastatic carcinoma.

Among 30 cases of multiple myeloma in the surgical pathologic laboratory there were 14 with leading symptoms involving the spine. Multiple myeloma is a tumor of adult life, the period of its greatest incidence being the sixth decade. The pain in 70 per cent of all cases (Geschickter and Copeland) begins in the lumbar and in the sacral region. In 40 per cent of cases compression of the spinal cord develops. These considerations justify the inclusion of multiple myeloma in a group of tumors affecting the spinal column.

The roentgenogram is often diagnostic. The lesions are rarefied punched-out areas and commonly produce pathologic fracture. They are multiple or become multiple in more than 95 per cent of cases. At times the punched-out areas may be seen in the vertebrae, but more often there is a pathologic fracture (fig. 4). Sacral lesions show the characteristic defects in the roentgenogram.

Because of the age at which its onset occurs and the multiplicity of its lesions, multiple myeloma is difficult to distinguish from metastatic carcinoma. Both, of course, are hopeless conditions, and the differential diagnosis is sometimes of academic interest only. The following points are useful: Metastatic carcinoma is by far the more common. The roentgen picture of multiple myeloma is the more distinctive. The fact that Bence Jones bodies are present in the urine is in favor of a diagnosis of multiple myeloma, and their absence would suggest a diagnosis of metastatic carcinoma, though they may or may not be present with either condition. The presence of chronic nephritis, with nitrogen retention and high serum proteins, is definitely favorable to a diagnosis of multiple myeloma. Biopsy is the last resort. Roentgen therapy is the treatment of choice for both conditions. The lesions of multiple myeloma respond more rapidly than do those of metastatic carcinoma.

Hodgkin's granuloma, lymphosarcoma, myeloid tumors and the xanthomatous lesions were found to be rare or absent in our series of

spinal tumors. Craver and Copeland<sup>6</sup> reported osseous changes in 15.7 per cent of 172 cases of Hodgkin's disease. Vertebral changes are said to be most frequent in cases with skeletal involvement, and these lesions may be either osteolytic or osteosclerosing. Neurologic symptoms are common. High voltage roentgen therapy causes remission of the symptoms, but permanent cure is not established.

There was a single lymphosarcoma in the present series. Craver and Copeland<sup>7</sup> found that bone was involved in 10.4 per cent of 164 cases. They also found that the spine was the most frequent site and that either an osteolytic or an osteosclerotic process may be present. As with Hodgkin's granuloma, compression of the spinal cord may develop. The tumor is radiosensitive.



Fig. 4.—Multiple myeloma of the spine. The twelfth thoracic vertebra is destroyed, and the lumbar spine is displaced laterally. The first lumbar vertebra also shows marked rarefaction.

Various types of myeloid tumors may produce changes in bone. These occur in myeloid and lymphoid leukemia, but so uncommonly that they need only be mentioned here. The osseous changes associated with chloroma are prominent but we found no instance of such involvement of the spine. Porosity and trabeculation of bone occur in erythroblastosis, and in the vertebral bodies these trabeculations tend to be vertical. One such tumor was included in this series.

Hand-Schüller-Christian disease produces circular osseous defects, usually multiple but occasionally single. The skull and the flat bones

6. Craver, L. F., and Copeland, M. M.: Changes in the Bone in Hodgkin's Granuloma, *Arch. Surg.* 28:1062 (June) 1934.

7. Craver, L. F., and Copeland, M. M.: Lymphosarcoma in Bone, *Arch. Surg.* 28:809 (May) 1934.

are most often affected. When a vertebral body is involved, collapse of that body occurs. We had 1 such case. Anspach<sup>8</sup> reported a case, the patient being a 5 year old boy, in which the body of the tenth thoracic vertebra was involved. Triangular collapse of this body occurred, but with clearcut edges, which distinguished the condition from tuberculosis. With irradiation the lesions of the bone heal in most instances.

#### BENIGN PRIMARY TUMORS OF THE VERTEBRAL COLUMN

The second largest group of spinal tumors is composed of primary tumors of the vertebral column, which numbered 58 in this series. The relative frequency of the various tumors is listed in table 3.

In all there were 37 benign lesions and 21 malignant lesions affecting the spinal column. Among benign tumors the most common are giant

TABLE 3.—*Primary Tumors of the Vertebral Column*

	Types of Tumor	Number of Cases
<b>Benign</b>		
Giant cell tumor.....		15
Osteochondroma.....		10
Bone cysts.....		7
Chondroma.....		3
Hemangioma.....		2
<b>Malignant</b>		
Osteogenic sarcoma		
Chondrosarcoma.....		8
Osteolytic sarcoma.....		4
Sclerosing sarcoma.....		4
Chordoma.....		5
Benign.....		37
Malignant.....		21
Total.....		58

cell tumor (in which type benign bone cysts may be included) and osteochondroma. This corresponds to the relative incidence of these tumors in the rest of the skeleton.

*Giant Cell Tumors.*—There were 15 giant cell tumors in the present series. In 1935 Murphy<sup>9</sup> collected 45 from the literature and pointed out that the typical history is characterized by injury to the spine in a young adult, followed by pain, tumor and occasionally kyphosis. Symptoms of pressure on the spinal cord may develop. The age incidence in our series is in accord with the findings of Murphy. Most of the patients were young adults. One girl, however, was 7 years of age and one man 62. The incidence of the condition in the male sex exceeded its incidence in the female sex in the proportion of 9 to 5.

8. Anspach, W. E.: Xanthomatosis with Involvement of a Vertebral Body, *Am. J. Dis. Child.* 48:346 (Aug.) 1934.

9. Murphy, G. W.: Giant Cell Tumor of the Spine, *Am. J. Roentgenol.* 34: 386, 1935.

Eight patients complained only of pain in the back. In 5 instances the pain in the back was followed by compression of the spinal cord. In 1 case the only symptoms were those of pressure on the spinal cord, and in the remaining case the symptoms of this compression preceded the pain in the back. In 6 cases a mass was present. The symptoms and signs depend, of course, on the portion of the vertebra which is involved and on the direction taken by the tumor in its growth.

The roentgenologic picture is variable but often diagnostic. As with tumors of the long bones, the other lesions with which giant cell tumor may be confused are hemangioma of the bone and chondroma. Chondroma usually may be excluded because of its rare occurrence in the spine. Hemangioma has the appearance of giant cell tumor when the neural arch or its processes are involved. Hemangioma of the vertebral body, however, has a very characteristic appearance (fig. 13).

Giant cell tumor may affect any portion of a vertebra, but in our cases it involved the neural arch or its appendages more frequently than it involved the vertebral body. Lewis<sup>10</sup> also found this to be true in the cases reviewed by him. Only 1 tumor occurred in the cervical region. The tumors occurred with equal frequency in the other regions of the spine. The roentgenogram may show a rarefied lesion which reduces the portion of bone involved to a barely visible shadow (fig. 5). In the sacrum the margins are usually clearcut (fig. 6). The trabeculations characteristic of giant cell tumor in long bones may be present and may indicate a healing reaction. The typical expansile trabeculated type of tumor is best seen when the lesion involves a transverse or a spinous process. A tumor of the neural arch may go into the spinal canal and may be very difficult to detect by roentgen examination. Giant cell tumor involving the body of a vertebra is very likely to cause destruction with collapse (fig. 7). Clearcut concave edges can be seen. Figure 7 also illustrates the nature of the shadow visible in the soft tissues. No trabeculations are visible, yet it is clearly seen that this is an expansile, noninfiltrating type of tumor. Figure 8 shows the absence of the shadow in the soft tissues after surgical intervention and the healing reaction after roentgen therapy.

Giant cell tumor of the spine, in spite of its benign character, may cause death. Of the 14 patients, 9 recovered. The causes of death in 3 cases were damage to the spinal cord, invasion of the inferior vena cava and hemorrhage. In 1 case the tumor had infiltrated the soft parts extensively at the time the patient was last seen. In the remaining case the patient died from another cause before the giant cell tumor had healed.

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10. Lewis, D.: Primary Giant Cell Tumor of the Vertebrae. *J. A. M. A.* 83:1224 (Oct. 18) 1924.



Fig. 5.—Giant cell tumor of the spine. The roentgenogram shows an extensive process of rarefaction, involving chiefly the third and fourth lumbar vertebrae. The fourth lumbar vertebra is almost entirely destroyed. The third lumbar vertebra shows only as a poorly defined shadow. A portion of the neural arch of the second lumbar vertebra is also destroyed. (Case of Dr. B. S. Putts, Erie, Pa.)

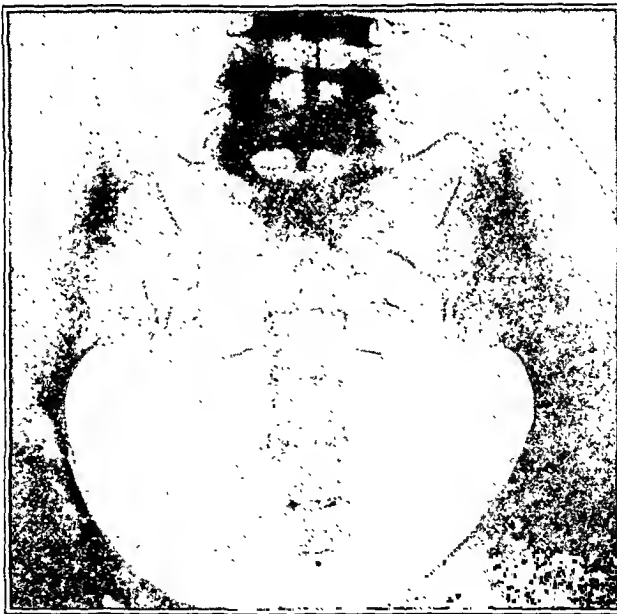


Fig. 6.—Giant cell tumor of the sacrum. The roentgenogram shows a rarefied area in the upper right half of the sacrum. The margins are clearcut, and faint trabeculations are visible. (Case of Dr. G. E. Bennett, Baltimore.)



Fig. 7.—Giant cell tumor involving the cervical vertebrae. The roentgenogram shows almost complete destruction of the body of the fourth cervical vertebra, with collapse and partial destruction of the bodies of the third and the fifth cervical vertebrae. There is also an expansile nontrabeculated mass in the prevertebral region pushing the larynx and trachea anteriorly. (Case of Mr. G. R. Girdlestone, F.A.C.S., Oxford, England.)

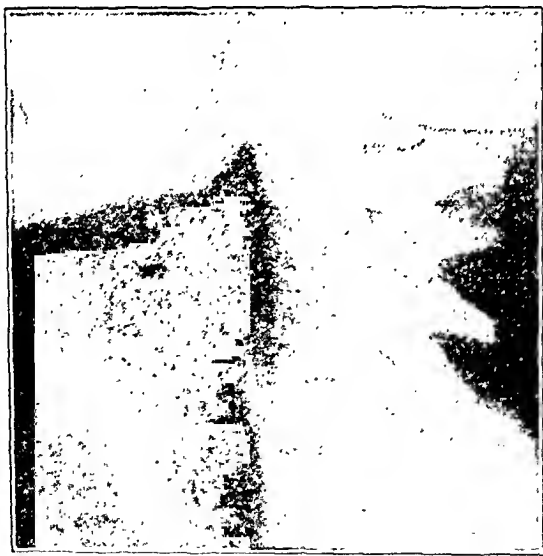


Fig. 8.—Giant cell tumor seen in figure 7, eleven months later. The tumor has been treated by curettage followed by irradiation. Notice the disappearance of the mass in the soft tissue and the healing reaction in the involved vertebrae.

Giant cell tumor may be diagnosed from the roentgenograms and treated with roentgen irradiation. In some cases operative procedures are necessary in order to relieve compression of the spinal cord or to stabilize the spinal column and prevent compression. An "aspiration biopsy" can be done and is not contraindicated in doubtful cases.

*Bone Cysts.*—In view of the relative frequency of giant cell tumor of the spine, one would expect bone cysts to be more common in this location. This, however, is not the fact. Multiple involvement of the spine, with bone atrophy and cyst formation, occurs as part of the syndrome of generalized osteitis fibrosa. There were 5 instances of such lesions. In 2 of these cystic lesions of the spine complicated the generalized skeletal deformity. In both of these cases pain in the back of increasing severity, was followed by signs of compression of the spinal cord. The roentgenologic picture showed diffuse atrophy of bone, bending deformities of the spine (most commonly kyphosis and scoliosis) and rarefaction and expansion of the bodies of one or more vertebrae or of a portion of the neural arch. In 3 other cases of generalized osteitis fibrosa demineralization and bending deformity of the spine were not accompanied by formation of the cysts.

No histologically verified solitary bone cysts of the spine, such as are commonly found in the shaft of the long bones in children, were recorded in this series. There was 1 such cyst occurring at the sacroiliac joint. In another instance a patient had been previously operated on for benign giant cell tumor, and at a second operation a similar lesion which had undergone cystic change was found above the original site. Microscopically this appeared to be a giant cell variant of the bone cyst. The absence of typical bone cysts in association with tumors of the spinal column lends support to the opinion that the usual bone cyst of the long bones is a benign giant cell tumor which has undergone healing. The failure of such a healing reaction to follow giant cell tumors of the vertebrae is explained by the cancellous structure of the vertebrae and by the absence of a well defined cortex of compact bone. The less rapidly growing giant cell tumors may take on a histologic character which justifies their classification as giant cell variants of the bone cyst, but active giant cell tumor tissue is rarely absent.

*Osteochondroma.*—Benign exostoses, which are so common in the remainder of the skeleton, are next in frequency. There were 10 of these in this series. Two were multiple exostoses affecting the remainder of the skeleton as well; the other 8 were all solitary lesions. With 2 exceptions the tumors arose from the neural arch or from one of its processes. In 3 cases the tumor projected into the spinal canal and gave rise to the symptoms of compression of the spinal cord. Case 4 is an instance of intraspinal osteochondroma.

CASE 4.—A woman complained of pain in the left leg present for eight years and of limping present for six months. There was tenderness in the lumbosacral region. Roentgen examination in November 1933 showed a dense mass, with a regular outline, filling the left side of the spinal canal at the level of the fifth lumbar vertebra (fig. 9). In December an osteochondroma was removed from the spinal canal. The patient was well on discharge from the hospital. Follow-up was not possible.

The roentgenologic picture of this tumor is typical of osteochondromas elsewhere. The more cartilaginous tumors might be confused with giant cell tumor. Such a condition is shown in figure 10. This tumor was irradiated and cartilaginous tissue was replaced by bone.



Fig. 9 (case 4).—Intraspinal osteochondroma, showing a dense mass filling the left side of the spinal canal at the level of the fifth lumbar vertebra. (Case of Dr. L. Y. Dryenforth, Jacksonville, Fla.)

One of the 10 patients died as a result of damage to the spinal cord. Excision is required only for those tumors presenting symptoms.

There was in the series 1 nucleus pulposus protruding into the spinal canal. This nucleus pulposus had become calcified and was shown in the roentgenogram as a dense rounded mass 1.5 cm. in diameter. Compere and Keyes<sup>11</sup> mentioned calcification of the extruded nucleus pulposus in their studies on the intervertebral disk.

11. Compere, E. L., and Keyes, D. C.: Roentgenological Studies of the Intervertebral Disc: Discussion of Embryology, Anatomy, Physiology, Clinical and Experimental Pathology, *Am. J. Roentgenol.* 29:774, 1933.



*Chondroma.*—Camp, Adson and Shugrue<sup>12</sup> stated that chondroma of the spinal column is rare. In this series there was but 1 chondroma which was examined microscopically (case 5).

CASE 5.—A white man aged 23 complained of pain in the lower part of the back, difficult urination and constipation, present for four months. Rectal examination disclosed a mass anterior to the sacrum. Roentgen examination (film not available) four months after the onset was reported as showing a “diffuse shadow” in the sacral region. Seven months after the onset a colostomy was performed for intestinal obstruction. The patient died four and one-half years after the onset, and postmortem examination revealed a large, smooth encapsulated tumor arising from the sacrum and projecting into the pelvis but not obstructing the intestine. The microscopic diagnosis was chondroma.

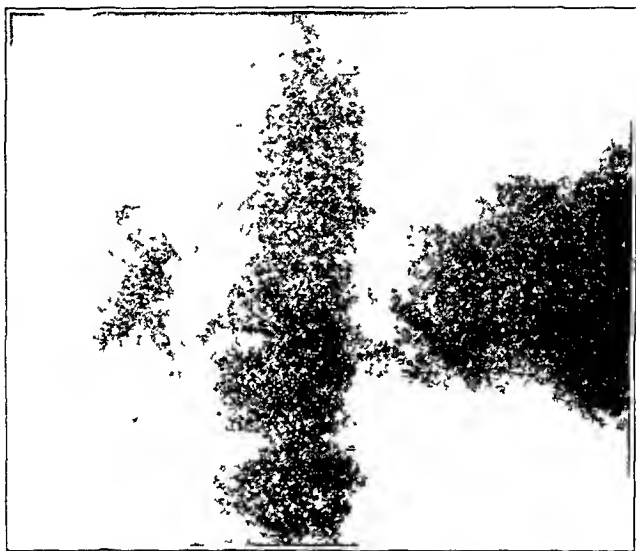


Fig. 10.—Osteochondroma involving a transverse process of the first lumbar vertebra. The tumor is well circumscribed and contains fine trabeculations. (Bone Registry American College of Surgeons no. 21.)

We cannot be sure of the diagnosis. No sections are available, and it is well known that chondrosarcoma and chordoma may be mistaken for chondroma. Examination of 2 other patients with tumors which are included in this group showed large rarefied areas in the sacrum, with cleancut margins. In neither case was the diagnosis proved by microscopic examination, and it may well be that the growths were giant cell tumors and not chondromas. Their slight response to irradiation

12. Camp, J. D.; Adson, A. W., and Shugrue, J. J.: Roentgenographic Findings Associated with Tumors of the Spinal Column, Spinal Cord, and Associated Tissues, *Am. J. Cancer* 17:348, 1933

suggests that they were chondromas. The patient whose condition is illustrated in figures 11 and 12 was under treatment with roentgen therapy for nine years. During this time the tumor showed an increase in size. It gives the impression of a chondroma.



Fig. 11.—Chondroma of the sacrum. The roentgenogram shows a well circumscribed, markedly trabeculated tumor involving the upper right half of the sacrum and extending over into the adjacent ilium.



Fig. 12.—Chondroma seen in figure 11, nine years later. The tumor was irradiated. Notice the extension of the tumor into the pelvis and into the adjacent ilium.

The absence of a certain diagnosis of chondroma for any growth in this series emphasizes the rarity of this tumor in the spine. A tumor displaying a roentgen picture of this type should be diagnosed as giant cell tumor. Irradiation should be tried, but it is less effective as a rule than for giant cell tumor.

*Hemangioma.*—Bucy and Capp<sup>13</sup> have contributed an excellent article on primary hemangioma of bone. They pointed out that when the vertebral bodies are involved vertical striations are produced which form an easily recognized roentgenologic picture (fig. 13). When a hemangioma involves a flat bone, such as the sacrum, a marked sunray effect is produced in the periosteal zone. This periosteal reaction is so marked and so regular that it may be distinguished from the somewhat similar picture of sclerosing osteogenic sarcoma in the same region. They also stated that the affected bone does not collapse and produce pain but that the first symptoms are those of compression of the spinal



Fig. 13 (Bone Registry American College of Surgeons no. 940).—Multiple hemangioma of the vertebral bodies. The roentgenogram shows vertical striations in the bodies of the third, the fifth and the sixth thoracic vertebrae. (Courtesy of Dr. P. C. Bucy and Dr. C. S. Capp.)

cord. The histories of the 2 hemangiomas in our series support this statement. One tumor affected the laminae; the other, the transverse process. The latter case is reported below.

CASE 6.—A white man aged 55 suffered pain in the left thigh for two and one-half years and loss of control of the bladder for three and one-half months. Saddle anesthesia and hyperactive reflexes were present. The Queckenstedt test

13. Bucy, P. C., and Capp, C. S.: Primary Hemangioma of Bone with Special Reference to Roentgenologic Diagnosis, *Am. J. Roentgenol.* **23**:1, 1930.

gave positive results. Roentgen examination in September 1927 revealed an expansile trabeculated tumor of the left transverse process of the first lumbar vertebra. A diagnosis of giant cell tumor was made, and at operation a hemorrhagic tumor involving the left transverse process and pedicle of the first lumbar vertebra was found. The tumor was removed with the curet. Microscopic examination revealed a cavernous hemangioma of bone.

It is interesting to note that the roentgen picture in case 6 was that of an expansile, trabeculated tumor resembling giant cell tumor (this emphasizes the variability of the roentgen pictures produced by hemangiomas involving the vertebral column). The histologic picture is almost invariably that of cavernous angioma, and the tumor responds readily to irradiation. Laminectomy, of course, is indicated when there are signs of compression of the spinal cord.

The small number of hemangiomas of bone in this series is not a true indication of its frequency. This indicates, instead, how infrequently symptoms are produced. Bucy and Capp stressed this point in their article, citing the work of Töpfer.<sup>14</sup> Töpfer in 2,154 autopsies found hemangiomas of the vertebral bodies in 257 instances (11.4 per cent); there were multiple growths in 34.

Only 1 angioma arising outside the spine and producing osseous changes was found. It arose in connection with the dura. The roentgenogram was reported as showing "a bulging of the bony framework of the cervical spinal canal." At operation an extradural hemangioma was disclosed which caused the laminae on the left side to bulge laterally and dorsally.

#### MALIGNANT PRIMARY TUMORS OF THE SPINAL COLUMN

Malignant primary tumors of the spinal column are less common than benign growths. There are but two types: osteogenic sarcoma and chordoma. Osteogenic sarcoma includes chondrosarcoma and the osteolytic and sclerosing types of sarcoma.

*Chondrosarcoma.*—There were 8 cases of chondrosarcoma of the spine. In 3 the tumor was single and primary; in 2 the growths were multiple but behaved like primary tumors; and in the remaining cases the sarcomatous change occurred in multiple exostoses (2 cases) or in Paget's disease (1 case). Excluding consideration of the time of appearance of the secondary chondrosarcomas, the average age of the patient at the onset was approximately 25 years. In 2 cases the only symptom was pain in the back, in 3 pain in the back was followed by symptoms

14. Töpfer, D.: Ueber ein infiltrierend wachsendes Hämangiom der Haut und multiple Kapillarektasien der Haut und inneren Organe: Zur Kenntnis der Wirbelangiome, Frankfurt. Ztschr. f. Path. 36:337, 1928.

of pressure on the spinal cord, in 1 these symptoms preceded the pain in the back. Detailed histories were not available in the 2 remaining cases. In 5 cases death occurred from three months to three years after the onset. One patient is living seven years after the onset. The tumor is growing slowly at the present time. Two patients have not been traced. The tumors occurred in all portions of the spine. Cases 7, 8 and 9 illustrate the varying types of chondrosarcoma.

*CASE 7.—Single primary lesion.*

A white man aged 35 complained of pain in the back following an injury in May 1935. Roentgen examination of the spine in September revealed no abnormality, but further examination in December showed partial destruction of the body of the ninth thoracic vertebra with a faint paravertebral fusiform shadow



Fig. 14 (case 7).—Primary chondrosarcoma of a thoracic vertebra. The roentgenogram shows destruction of the body of the ninth thoracic vertebra without any appreciable collapse. A faint paravertebral fusiform shadow is visible. (Case of Commander H. E. Ragle [MC], U. S. Navy, Washington, D. C.)

(fig. 14). Spastic paralysis of the lower extremities developed in February 1936. In March a hemathorax was discovered, and tubercle bacilli were found in the sputum. Tuberculosis of the spine was considered the probable diagnosis. A roentgen examination at this time revealed an increase in the paravertebral shadow. The patient died in November, and at postmortem examination the region extending from the eighth thoracic vertebra to the tenth was found to be the site of a chondrosarcoma which had destroyed the spine and the spinal cord and had metastasized to the lungs.

*CASE 8.—Multiple primary lesions.*

A white girl aged 14 complained of difficulty in walking present nine months and of pain in the back and inability to flex the muscles of the neck present for one month. This condition progressed to a flaccid paralysis of both lower extremi-

ties. There was tenderness over the sixth thoracic vertebra. Roentgen examination in July 1931 revealed paravertebral spotty calcified areas in the upper dorsal region (fig. 15). Laminectomy at this time disclosed nodular cartilaginous masses external to the laminae and within the spinal canal. The patient died in November. Permission for autopsy was not obtained.

In a case similar to case 8 an autopsy was performed and multiple cartilaginous tumors were found affecting almost the entire skeleton. Figure 16 is a photograph of the lesion as seen at autopsy. It is probable that a roentgenogram in this case would have simulated that in case 8 (fig. 15). These 2 cases are peculiar in that multiple tumors arose simultaneously and were apparently not secondary changes occurring in preexisting multiple exostoses.



Fig. 15 (case 8).—Primary chondrosarcoma of the upper thoracic spine with multiple lesions. The roentgenogram shows paravertebral, spotty calcified shadows. (Case of Dr. George Armstrong, Ottawa, Ontario, Canada.)

CASE 9.—*Secondary sarcomatous change in a preexisting multiple lesion.*

A white woman aged 41 had had multiple exostoses as long as she could remember. Pain in the back had been present for three years and a palpable mass in the lumbar region for one year. Roentgen examination in May 1921 revealed the shadow of a mass in the soft tissues in the right lumbar region, containing many irregular dense areas (fig. 17). Roentgen examination of the rest of the skeleton revealed benign exostoses of the tibia, the fibula, the femur, the radius and the ulna, with the characteristic deformity of the radius and the ulna. Exploration of the lumbar mass in August disclosed a cartilaginous cystic tumor, with many calcified areas. Radium was used postoperatively. The patient died in June 1923, and at autopsy a chondrosarcoma weighing 8 Kg. was found in the lumbar region with metastases to the liver and the lung.



Fig. 16.—Primary chondrosarcoma of the spine with multiple lesions. The photograph of the spine at autopsy shows multiple cartilaginous nodules in the paravertebral region of the thoracic spine.



Fig. 17 (case 9).—Chondrosarcoma of the spine secondary to benign exostoses. The roentgenogram shows a faint paravertebral mass lateral to the third, fourth and fifth lumbar vertebrae. Irregular dense areas are visible within the tumor.

*Osteogenic Sarcoma.*—Four osteolytic sarcomas and 4 sclerosing sarcomas are included in the present series. Two sarcomas of the osteolytic type were superimposed on Paget's disease. The average age of the patients was 25 years, excluding those with sarcomas complicating Paget's disease. The outstanding symptoms were those of pain in the back or pain at the nerve roots, which was frequently followed by compression of the spinal cord. All of the sarcomas terminated fatally, with an average duration of life of twenty-one months. With the exception of the tumor in 1 case of Paget's disease, in which the sarcomatous change extended throughout the length of the spine, all the growths arose in the sacrum or in the lumbar vertebrae.

Figures 18 and 19 contrast the roentgenographic changes associated with sclerosing and osteolytic sarcoma respectively. The sclerosing type (fig. 18) may be confused with hemangioma in the sacrum, but with hemangioma the sunray effect in the periosteal zone is usually more regular and more pronounced. With osteolytic sarcoma (fig. 19) a diffuse destructive process with irregular invasive margins is seen. Osteolytic sarcoma might be confused with giant cell tumor (fig. 6). When the sclerosing type of sarcoma extends into the soft parts, bone is produced. This is a conclusive finding in the roentgenogram (fig. 20).

High voltage roentgen therapy was given to 5 of the patients with osteolytic and osteosclerosing sarcoma. Life was not prolonged, but pain was relieved. Roentgen therapy was employed in 1 case of chondrosarcoma of the sacrum (single primary lesion), and the patient is alive six years after onset. Radium was implanted during the treatment of 1 secondary chondrosarcoma (sarcoma complicating multiple exostoses), and the patient died two years after the beginning of the treatment. Roentgen therapy is the treatment of choice for osteogenic sarcoma of the spine.

*Chordoma.*—Chordoma has been frequently reported in the literature. In 1935 Mabrey<sup>15</sup> gathered 150 cases from the literature. Eighty-seven of the chordomas in his cases were sacrococcygeal, 49 were cranial and the remaining 14 were distributed elsewhere along the vertebral column. Ribbert<sup>16</sup> in 1894 named the tumor. Most observers agree that the notochord, from which the tumor arises, is of entodermal origin. According to Mabrey's statistics, the age of greatest incidence of the sacrococcygeal tumors is from 40 to 60 years and of the speno-occipital

15. Mabrey, R. E.: Chordoma: A Study of One Hundred and Fifty Cases, *Am. J. Cancer* 25:501, 1935.

16. Ribbert, M. W. H.: Ueber die Ecchondrosis physaliflora spenooccipitalis, nach Untersuchungen von Hermann Steiner. *Centralbl. f. allg. Path. u. path. Anat.* 5:457, 1894.



tumors is from 20 to 40 years. He also stated that the average duration of life for these patients is twenty-eight and a half months, the extremes of age being 4 months and 18 years.

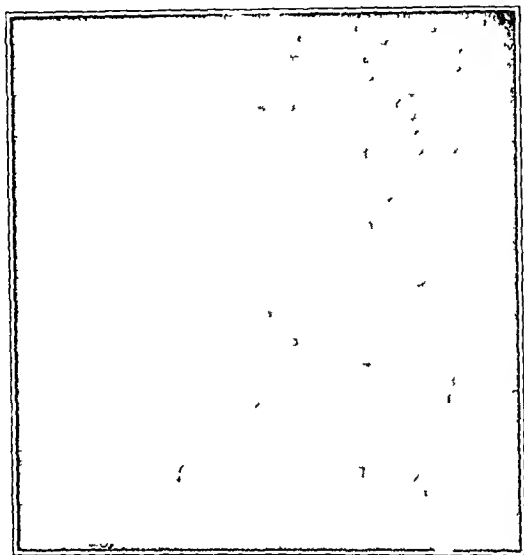


Fig. 18—Osteogenic sarcoma (sclerosing type) involving the sacrum and the adjacent ilium. The roentgenogram shows a sclerosing process which extends out into the soft parts in the form of radiating bony spicules

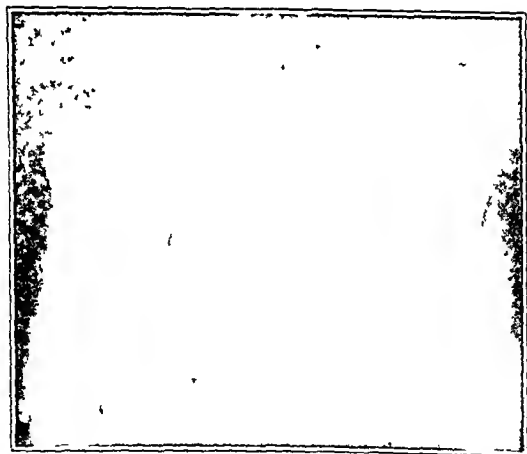


Fig. 19—Osteolytic osteogenic sarcoma of the sacrum. The roentgenogram shows rarefaction in the upper part of the sacrum, with irregular margins.

In the laboratory of surgical pathology there are records of 5 cases of chordoma. In 3 of these the tumor was sacrococcygeal, in 1 occipital and in the other cervical. The ages of the patients ranged from

26 to 71 years. The patients who had a tumor in the cervical or occipital region died from encroachment of the tumor on the central nervous system. A tumor in the upper part of the cervical region may produce nasopharyngeal or pharyngeal symptoms. One of the patients with sacrococcygeal tumor had lived nine years after onset when last seen. The tumor had been excised three times and had been treated with radium. Another patient with a growth of this type was living four years after the onset. The tumor had been twice excised and in spite of roentgen therapy was still growing and was considered inoperable. In the remaining case the tumor was twice excised, and at the second

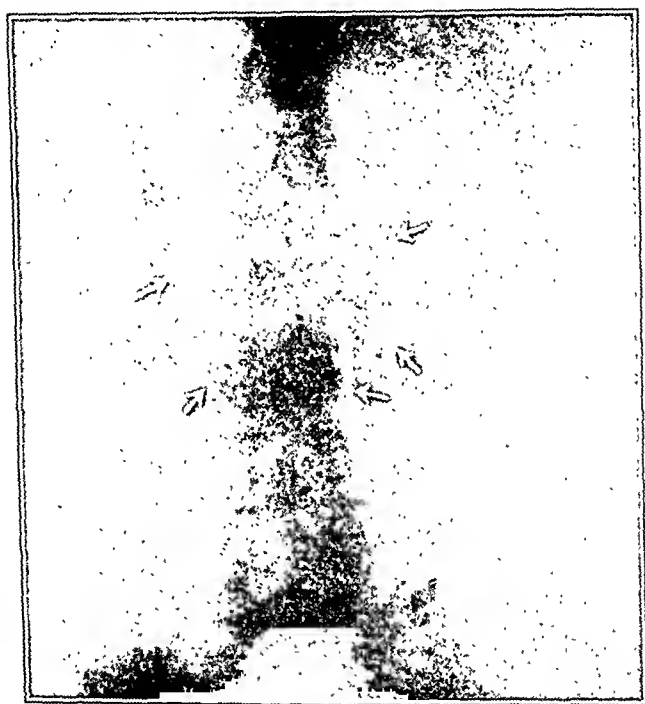


Fig. 20.—Osteogenic sarcoma of the lumbar spine. The roentgenogram shows marked destruction and sclerosis of the body of the second lumbar vertebra, with dense areas visible in the surrounding soft parts. Notice the absence of collapse of the body of the second lumbar vertebra. The adjacent vertebrae also show destructive and sclerotic changes.

operation metastatic nodules were removed from the soft tissue of the forearm, the arm, the hip and the pectoral region. This patient was not traced after the last operation.

The roentgenogram usually shows destruction of bone, with the shadow of a tumor in the soft tissues (fig. 21).

The tumor is slow growing but malignant and kills by invasion of vital structures. Mabrey estimated that at least 27 per cent of the

growths metastasize. There were metastases from 2 tumors in our series, to the regional lymph nodes in 1 instance and to distant soft tissues in the other.

The microscopic picture is variable. Alezais and Peyron,<sup>17</sup> basing their studies on the histogenesis of the notochord in the embryo, distinguished three general types. The first and most primitive type of chordoma, according to their studies, should correspond to that stage in which the notochord is evaginated from the entoderm. They could, however, find no tumor corresponding to this stage. A second and more clearly differentiated type of chordoma would be formed by solid cords of polyhedral and globular cells with abundant granular cytoplasm. Some of the cells show vacuolation. In our series 3 chordomas



Fig. 21.—Chordoma of the sacrum. The roentgenogram shows destruction of the lower portion of the sacrum, with a large intrapelvic mass (from previously published case, Harnos, O., and Palmer, L. A.: *Chordomata and Report of a Case*, *Virginia M. Monthly* 62:638 [Feb.] 1936).

were of this type (figs. 22 and 23). In the third stage these cells become increasingly vacuolated and a homogeneous intercellular mucinous matrix is produced. Two of the tumors in our series presented a microscopic picture corresponding to that of this adult type of chordoma (fig. 24).

Irradiation seems to have little effect on this type of tumor. Surgical excision may be attempted, but recurrence is the rule.

17. Alezais and Peyron. *Sur l'histogénèse et l'origine des chordomes*, *Compt. rend. Acad. d. sc* 171:419, 1922

## SYMPATHICOBLASTOMA (AND EWING'S SARCOMA)

No mention has been made of Ewing's sarcoma in the discussion of the primary malignant tumors of the vertebral column. The reason for this omission is found in the succeeding paragraphs.

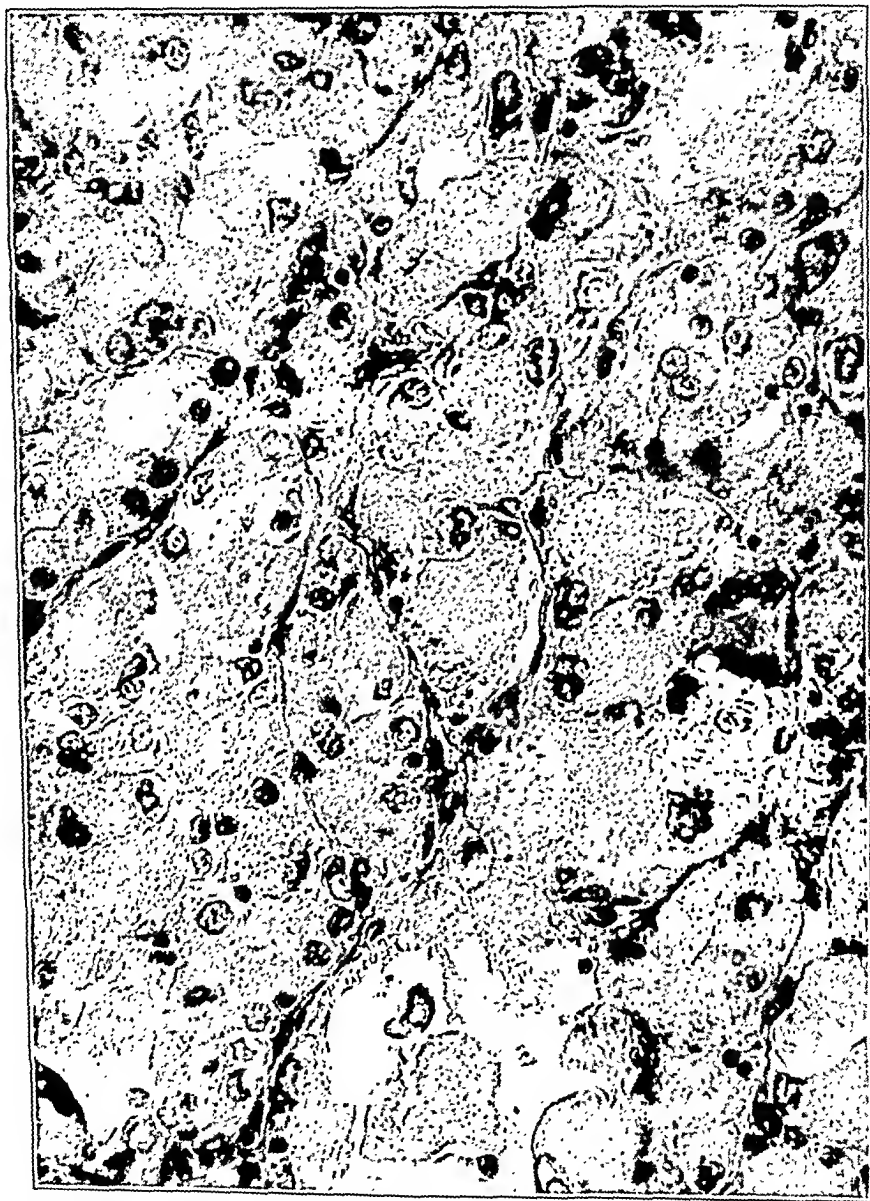


Fig. 22.—High power photomicrograph of a chordoma, showing large globular cells with abundant granular cytoplasm.

In a series of approximately 100 tumors involving the spinal cord, in the records of the department of neurosurgery of the Johns Hopkins

Hospital, there were 6 which affected bone and which on microscopic examination were found to be sympathicoblastomas. Records of 6 additional tumors of this type were found in the files of the laboratory of

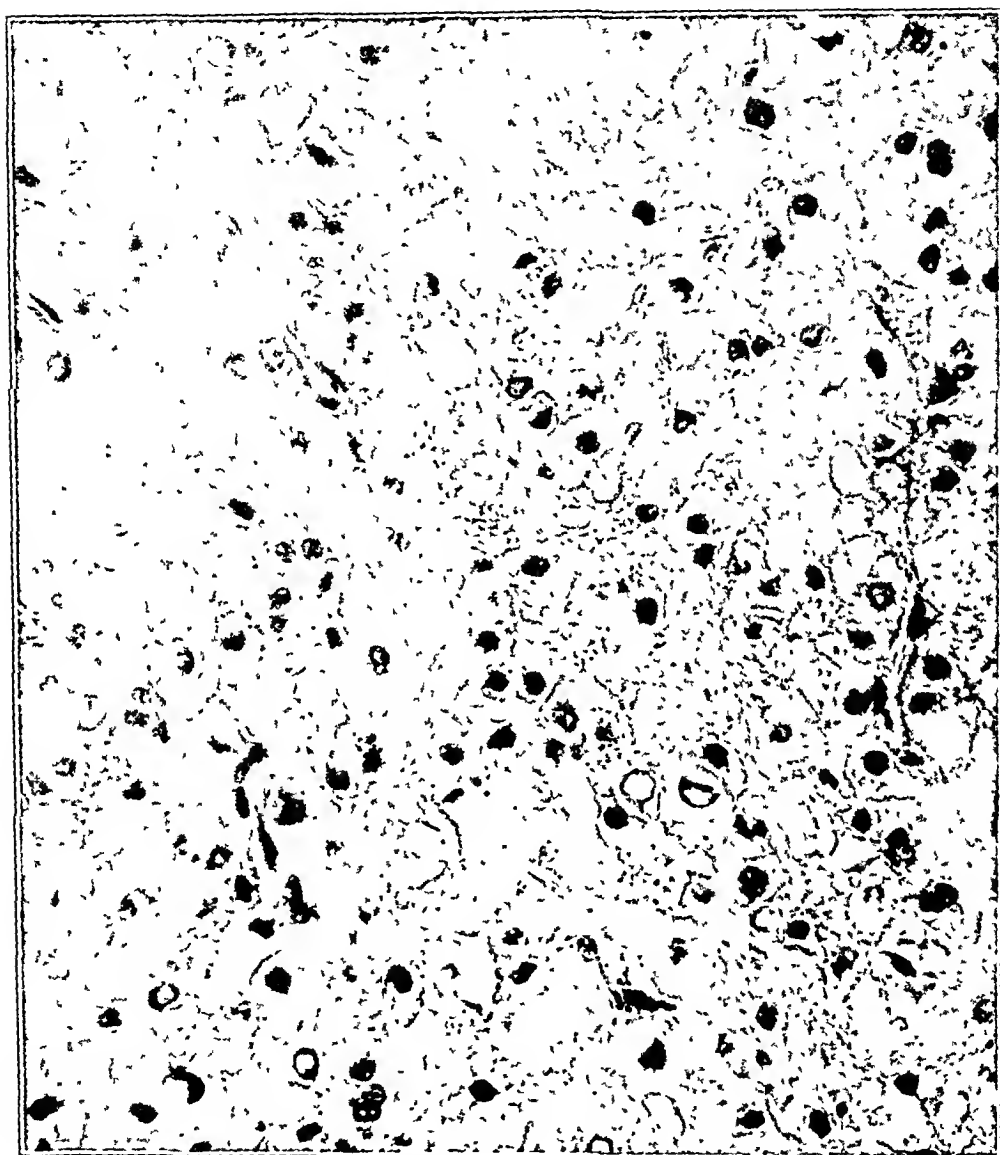


Fig. 23—High power photomicrograph of chordoma cells in the stage of vacuolization. (Case of Dr. W. S. Hastings, Fox Chase, Philadelphia.)

surgical pathology. These 12 tumors were types of sympathicoblastoma in all stages of differentiation. Summaries of the clinical histories of the cases are given at the end of the section describing the tumors.

The incidence of sympathicoblastoma in this series of spinal tumors was relatively high. This type of paravertebral tumor is not generally thought to complicate the diagnosis of neoplastic lesions about the vertebral column.

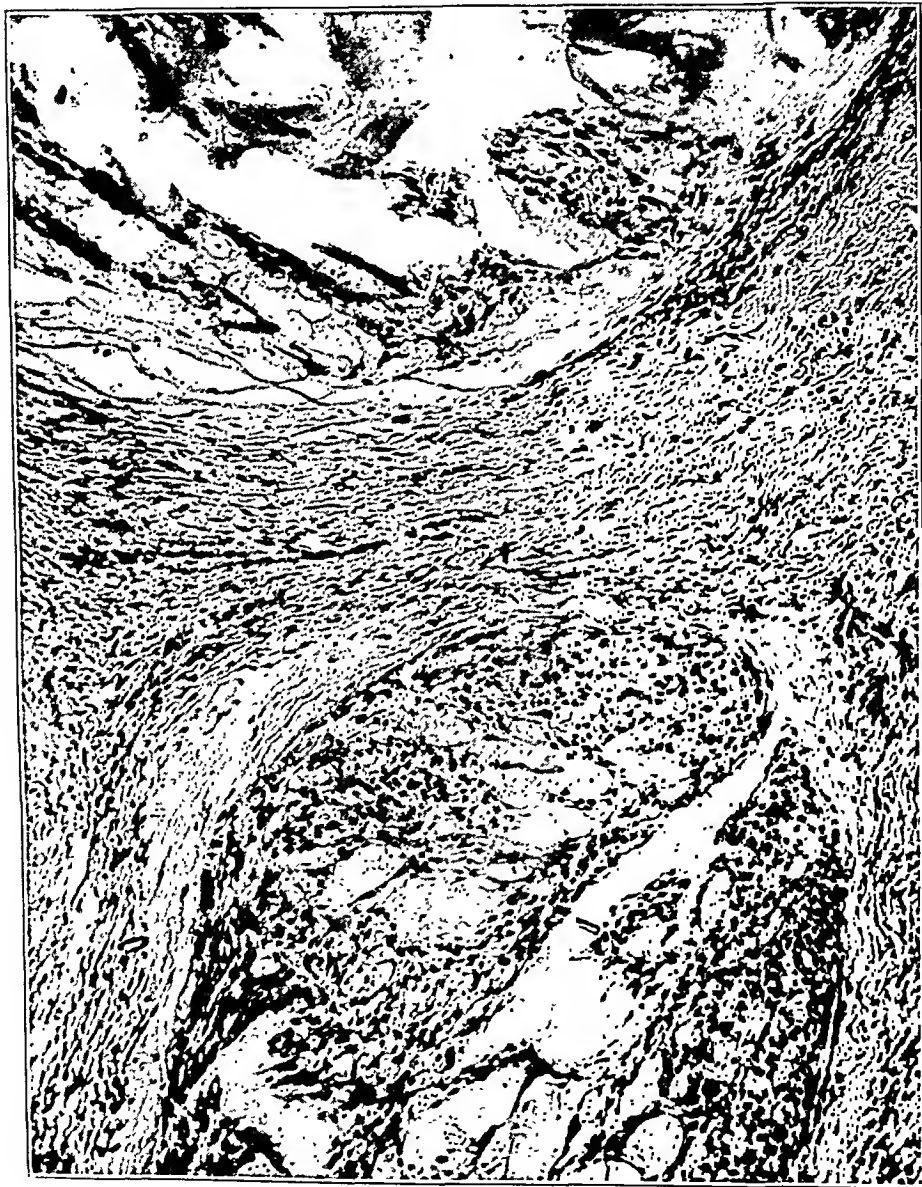


Fig. 24.—Low power photomicrograph of a chordoma in the adult stage. The chordomatous tissue is divided into lobules by fibrous septums. The lobules contain mucinous matrix and clusters of chordoma cells.

The average age of onset of these 12 sympathicoblastomas was 33 years, the extremes of age being 15 and 66 years. These ages appear

high, since sympathicoblastoma is generally a tumor of childhood and one of the commonest malignant tumors of that period. Scott and Palmer,<sup>18</sup> however, collected 32 cases of neuroblastoma arising from the sympathetic nervous system outside the adrenal medulla and found that the ages of the patients ranged from 1 month to 64 years. Schultz<sup>19</sup> tabulated 58 cases of benign ganglioneuroma and found that 26 of the tumors occurred in adults and 22 in children. The ages of 10 of the patients were not stated. Less clearly differentiated forms of neuroblastic tumor may also occur in adults (Wright;<sup>20</sup> Symmers;<sup>21</sup> Barnewitz;<sup>22</sup> Capaldi;<sup>23</sup> Busch;<sup>24</sup> Blumensaat<sup>25</sup>).

Both Schultz and Scott found the tumors more common among female than among male patients. In our series the incidence was equal in the two sexes.

The clinical histories in these cases were fairly uniform. The complaints were those of pain in the back, pain at the nerve roots or symptoms of compression of the spinal cord. Four patients showed symptoms of pressure on the spinal cord. In 6 others pain in the back preceded the onset of compression of the spinal cord. The remaining 2 had pain in the back as the only complaint. Pain at the nerve roots was an additional complaint of 5 patients. One expects, then, a tumor which destroys bone and presses on the spinal cord or on the nerve roots. Such is the case, as is seen by an examination of the roentgenologic, operative and postmortem evidence.

The roentgenogram showed a purely destructive lesion in 7 cases. In only 1 case was there a purely osteosclerotic lesion. In 3 cases osteolysis and osteosclerosis were both present. In addition, a paravertebral mass was visible in 4 of the roentgenograms. Figure 25 presents an example of osteosclerosis of the body of the tenth thoracic vertebra. In figure 26 a mass surrounded by a fairly well formed osseous

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18. Scott, E., and Palmer, D. M.: Intrathoracic Sympathicoblastoma: Report of a Case, *Am. J. Cancer* **16**:903, 1932.

19. Schultz, O. T.: Tumors of Neurogenous Origin, in Abt, I. A.: *Pediatrics*, Philadelphia, W. B. Saunders Company, 1926, vol. 8, p. 744.

20. Wright, J. H.: Neurocytoma or Neuroblastoma, a Kind of Tumor Not Frequently Recognized, *J. Exper. Med.* **12**:556, 1910.

21. Symmers, D.: A Recurrent Neuroblastoma of the Scapular Region, *J. A. M. A.* **60**:337 (Feb. 1) 1913.

22. Barnewitz: Zur Kenntnis des Neuroblastoma sympathicum, *Frankfurt. Ztschr. f. Path.* **26**:317, 1921.

23. Capaldi, B.: Zwei Fälle von Sympathikoblastom, *Frankfurt. Ztschr. f. Path.* **35**:83, 1927.

24. Busch, E.: On Ganglioneuroblastoma Sympathicum, *Acta path. et microbiol. Scandinav.* **5**:289, 1928.

25. Blumensaat, C.: Zur Kenntnis der Neuroblastome des Sympathicus beim Erwachsenen, *Virchows Arch. f. path. Anat.* **269**:431, 1928.



Fig. 25 (case 16).—Sympathicoblastoma. The roentgenogram shows increased density of the body of the tenth thoracic vertebra with a paravertebral fusiform shadow. (Case of Dr. J. W. Riley, Oklahoma City.)



Fig. 26 (case 21).—Sympathicoblastoma. The roentgenogram shows destruction of the transverse process and pedicle of the third lumbar vertebra, with a paravertebral mass surrounded by a bony shell. (Case of Dr. H. R. Bohlman, Baltimore.)



shell is visible. This view also shows destruction of the left transverse process and pedicle of the third lumbar vertebra. Figure 27 is a roentgenogram of a postmortem specimen. The tumor stimulated reactive bone, thus producing the radiopaque area seen in the region of the spinal canal. These osteosclerotic changes may take place in the substance of the bone or may occur as a periosteal reaction.

The *sympathicoblastomas* in this series occurred in the thoracic or lumbar portion of the spine, with the exception of the tumor in case 10, which involved both the cervical and the thoracic region. Autopsy was

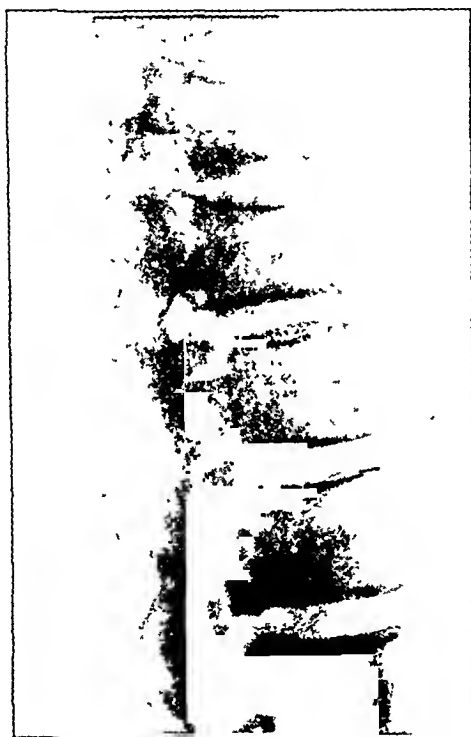


Fig. 27 (case 14).—Gangliosympathicoblastoma. The roentgenogram was taken of the postmortem specimen. It shows an osteosclerotic lesion in the region of the neural arch and spinal canal.

performed in only 50 per cent of the cases, but from correlation of the roentgenologic and the operative findings it is evident that there was a paravertebral mass (fig. 32) lying on the bodies of the vertebrae in 10 cases. One of the 10 tumors was a metastasis from the adrenal gland (case 15), but since it acted like a paravertebral tumor we have included it in this series. Of the 2 remaining tumors, 1 was intradural (case 18) and the other extradural (case 17). This intraspinal location is of frequent occurrence, since all the neuroblastic cells must migrate

peripherally from the primitive neural tube, and it is possible for a tumor to develop at any point between their site of origin and their destination.

Of the 10 tumors in the paravertebral region, 8 had extended into the spinal canal through an intervertebral foramen. In every instance bone was affected. These two features account for the clinical picture produced.

When seen at operation or at autopsy the tumors are friable, hemorrhagic and sometimes necrotic. Often they are fairly well circumscribed, though not encapsulated. One tumor (case 10) was described as having a polypoid appearance. There is a definite tendency of the tumor to extend in this serpiginous fashion. This is well shown by its extension into the spinal canal.

In this series of cases of sympathicoblastoma multiple metastases to bone occurred in 2 instances and a single metastasis to bone in 2 others. The lungs were involved in 4 instances. Metastasis to lymph

TABLE 4.—(from Blacklock<sup>26</sup>)

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I—Sympathicoblastoma (all malignant)
(A) Undifferentiated—composed only of sympathogonia
(B) Differentiated
1—Composed of sympathogonia and sympathoblasts
2—Composed of ganglion cells in addition to more primitive cells (ganglio-sympathicoblastoma)
II—Ganglioneuroma (generally simple) [and benign*]
Composed only of mature ganglion cells

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\* Added by authors.

nodes occurred in 1 case. Death without metastasis occurred in 1 case from fatal damage to the spinal cord. Three patients are alive without metastasis. In the remaining 2 cases follow-up was not possible.

The histologic picture of these tumors is variable. The growth may show neuroblasts in any stage of differentiation. An understanding of the histology must be based on histogenesis. Table 4 is a simple classification based on histogenesis which was offered by Blacklock.<sup>26</sup> The term sympathicoblastoma was suggested by Bailey and Cushing<sup>27</sup> in 1926 for the undifferentiated tumors of the sympathetic nervous system.

The differentiation of the adult tissues of the sympathetic nervous system has been described by such observers as Bielschowsky,<sup>28</sup> Schultz and Scott. The neuroepithelium of the primitive neural tube gives

26. Blacklock, J. W. S.: Neurogenic Tumors of the Sympathetic System in Children, *J. Path. & Bact.* 39:27, 1934.

27. Bailey, P., and Cushing, H.: A Classification of Tumors of the Glioma Group, Philadelphia, J. B. Lippincott Company, 1926.

28. Bielschowsky, M.: Neuroblastic Tumors of the Sympathetic Nervous System, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 1085.

rise to neuroblasts and glial cells. The neuroblasts of the sympathetic nervous system form sympathogonia. These are small cells with a round or oval hyperchromatic nucleus, scanty cytoplasm and at times delicate fibrils. As differentiation proceeds, the nuclei become larger and more

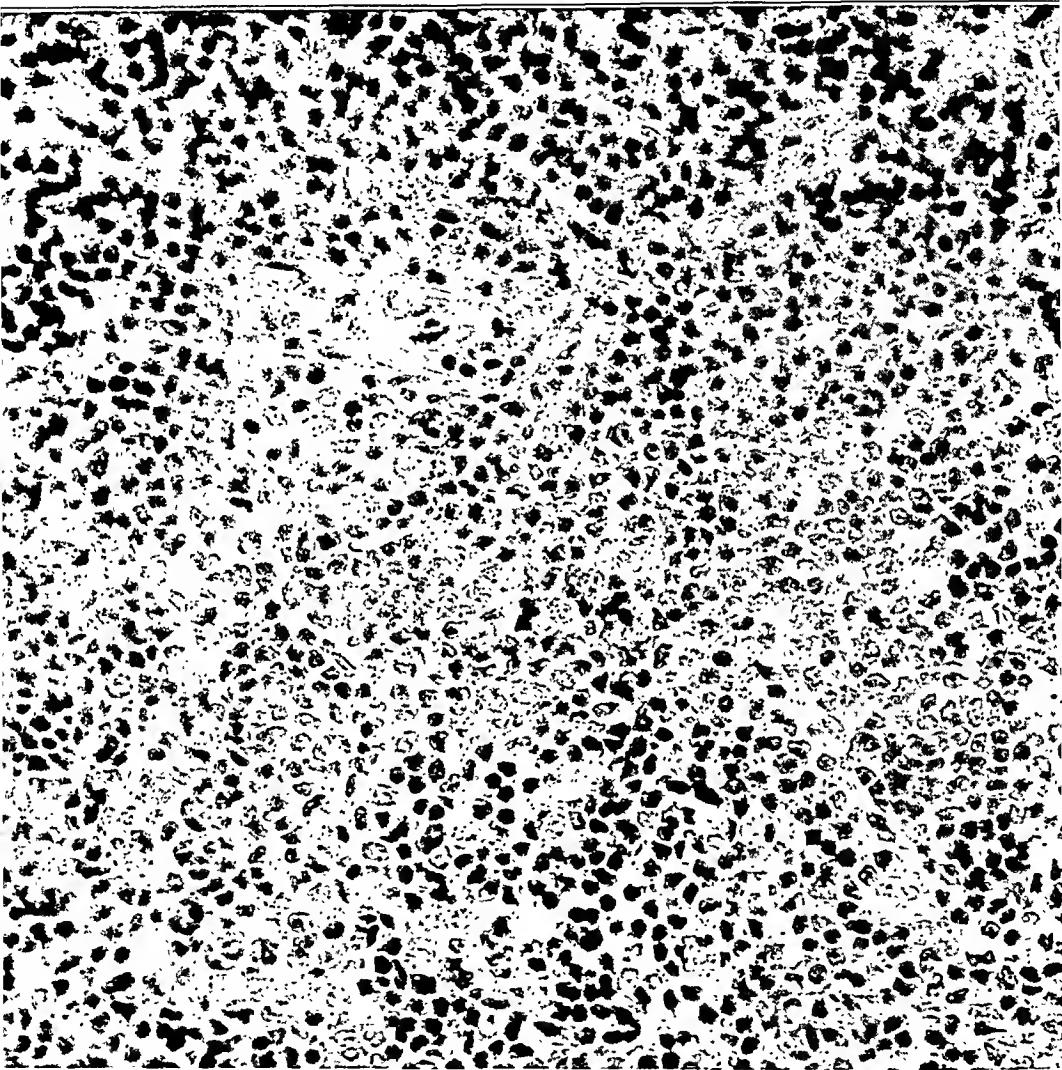


Fig. 28 (case 19).—High power photomicrograph of sympathicoblastoma, showing a cellular tumor consisting mostly of sympathogonia. A few sympathoblasts may be seen.

vesicular and the cytoplasm becomes more abundant. The cytoplasmic processes or the fibrils become prominent features. The cells are then sympathoblasts. As the cells approach the adult form, the nuclei are

enlarged and show large nucleoli; the cytoplasm increases and acquires Nissl granules. The cells are then ganglion cells.

The pheochromocyte of chromaffin tissue also differentiates from the sympathogonia. However, no tumors of this type occurred in the present series.

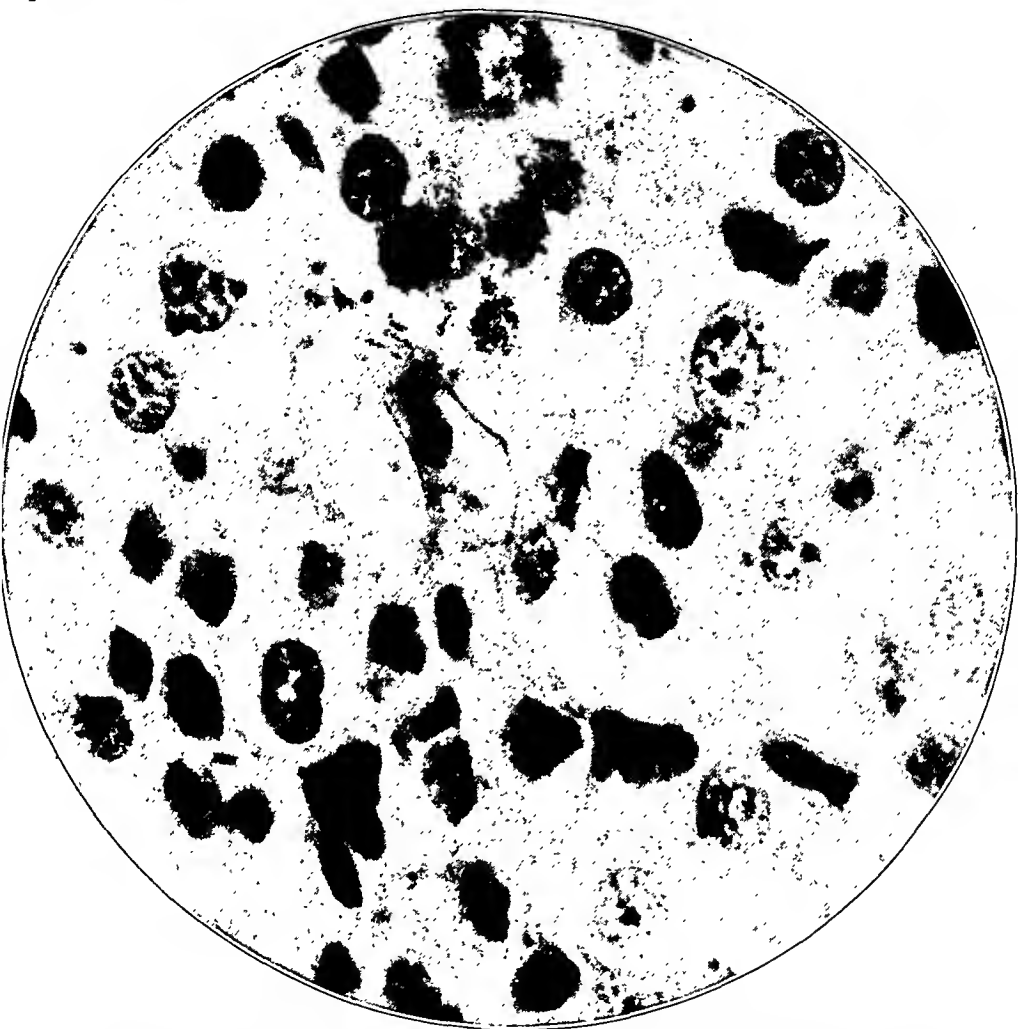


Fig. 29 (case 18).—High power (oil immersion) photomicrograph of a sympathicoblastoma, showing sympathoblasts with large vesicular nuclei and cytoplasm in processes.

A sympathetic neural tumor may arise from any of the types of cell described in the differentiation of the neuroblast. Sympathogonia and sympathoblasts are commonly present in the same tumor. All three types may be present (gangliosympathicoblastoma). Sympathogonia predominate in the undifferentiated sympathicoblastoma (fig. 28). Rosettes are few and are often indicated only by clumps or balls of cells (Blacklock).

When sympathoblasts are present in abundance, fibrils are usually a prominent feature (fig. 29). Rosettes are often present. The intermingling of the two types of cells, sympathogonia and sympathoblasts, forms a microscopic picture characteristic of the differentiated sympathicoblastoma (fig. 30). Well formed rosettes were not numerous

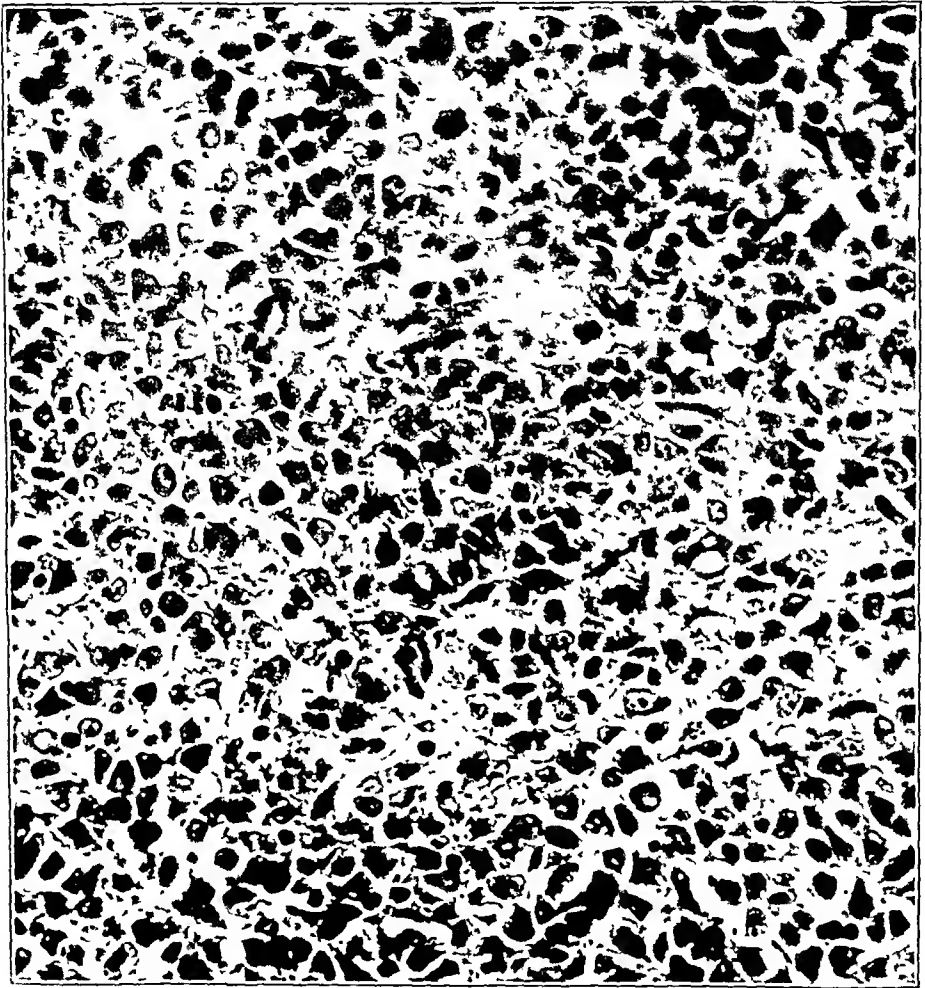


Fig. 30 (case 21).—High power photomicrograph of a sympathicoblastoma, showing sympathogonia and sympathoblasts.

in any of these tumors. Mitotic figures though present were not numerous.

When the adult ganglion cell is present, the tumor is easily identified (fig. 31). The gangliosympathicoblastomas usually contain less differentiated cells as well. In this section reactive bone and fibrosis were marked features.

The reaction of the sympathicoblastomas to treatment remains to be considered. Table 5 shows the duration of life of the patients and the type of treatment for this condition. Excision of the tumor fol-



Fig. 31 (case 14).—High power photomicrograph of a gangliosympathicoblastoma, showing adult ganglion cells some of which are embedded in bone.

lowed by irradiation is apparently the treatment of choice. The relatively long duration of life in case 14, in which the patient received no treatment, is explained by the fact that the tumor in that case was

of a more clearly differentiated and less malignant form than were the other tumors.

Table 5 indicates that sympathicoblastoma is radiosensitive. The patient in case 17 was well without recurrence of symptoms seven years after the operation. Irradiation was given postoperatively. Stewart<sup>29</sup> and also Colville and Willis,<sup>30</sup> have observed that neuroblastoma (sympathicoblastoma) responds to irradiation. This radiosensitivity is a characteristic of two other neuroblastic tumors, retinoblastoma (Moore<sup>31</sup>) and medulloblastoma (Cutler, Sosman and Vaughan<sup>32</sup>), both of which resemble sympathicoblastoma in histologic appearance.

*Ewing's Sarcoma.*—No tumors were found in this series which could unquestionably be diagnosed as Ewing's sarcoma of the spine. The remarkable similarities between this tumor and sympathicoblastoma

TABLE 5.—*Duration of Life of Patients and Type of Treatment in Cases of Sympathicoblastoma*

Case No.	Duration of Symptoms Prior to Treatment, Months	Duration of Life After Treatment, Months	Treatment	Result
12	..	72	Excision; irradiation	Patient died
17	5	84	Excision; irradiation	Patient well 1938
16	18	43	Excision; irradiation	Patient died
10	6	42	Excision	Patient died
13	2	21	Excision; irradiation	Patient died
11	6	12	Excision; irradiation	Patient died
19	1	7	Excision	Condition of patient improved 1937
21	18	4	Excision	Condition of patient improved 1937
15	6	0	None	Patient died
14	60	0	None	Patient died
20	3	..	?	Patient died
18	8+	?	Excision	No follow-up

account in some measure for this difficulty. The microscopic picture of Ewing's sarcoma and that of sympathicoblastoma are strikingly similar, and by the ordinary staining methods differentiation between the two is difficult. The reticulum cell variant of Ewing's sarcoma is not unlike a sympathicoblastoma in which sympathoblasts predominate. In addition, both types of tumor may respond to high voltage roentgen therapy. Both types of tumor also have a tendency to metastasize to one or more bones, to the lungs or to the lymph nodes.

29. Stewart, F. W.: Radiosensitivity of Tumors, *Arch. Surg.* **27**:979 (Dec.) 1933.

30. Colville, H. C., and Willis, R. A.: Neuroblastoma Metastases in Bones, with a Criticism of Ewing's Endothelioma, *Am. J. Path.* **9**:421, 1933.

31. Moore, R. F.; Stallard, H. B., and Milner, J. G.: Retinal Gliomata Treated by Radon Seeds, *Brit. J. Ophth.* **15**:673, 1931.

32. Cutler, E. C.; Sosman, M. C., and Vaughan, W. W.: The Place of Radiation in the Treatment of Cerebellar Medulloblastoma: Report of Twenty Cases, *Am. J. Roentgenol.* **35**:429, 1935.

The frequency with which multiple bone metastases are noted soon after the appearance of a primary Ewing sarcoma of bone has often been described as a characteristic of this tumor. The first clinical evidence of a sympathicoblastoma may be a metastatic lesion in the skull. Coleville and Willis observed the case of an 8 year old child who previous to death presented a typical picture of Ewing's sarcoma of the femur. The age, history, roentgen findings, observations at biopsy and response to irradiation were all consistent with this diagnosis. The child died five months after onset, and at autopsy a neuroblastoma of the adrenal was found, with multiple metastases to bone.

Since these two tumors are so similar, the question arises as to whether some of the tumors in our series diagnosed as sympathicoblastomas were not Ewing sarcomas of the spine. To be considered against this theory is the fact that these growths were paravertebral in origin, whereas Ewing's sarcoma usually begins in the bone proper. In general, the microscopic structure of the individual tumors is more variable than that of Ewing's sarcoma and corresponds to the structure of tumors of the sympathetic nervous system described in the literature, as well as to the structure of those studied in this laboratory. Because roentgenologic changes in the complex bony structure of the spine are not comparable to those in other bones, the roentgenologic changes characteristic of a Ewing sarcoma in the long bones do not aid in distinguishing between these two tumors in the spine.

On the other hand, the suggestion has been offered by some authors (Colville and Willis) that Ewing's sarcoma of bone is in some cases a metastasis from a sympathicoblastoma. Such mistakes in clinical diagnosis undoubtedly occur. The fact that a Ewing sarcoma may arise as a primary tumor of bone, however, is established by those cases in which the patient has been permanently cured by radical removal of the affected bone. Records of 5 patients with Ewing's sarcoma remaining well for periods varying from five to ten years after such surgical treatment are recorded in this laboratory.

From the considerations herein presented, however, it is apparent that further investigations are necessary, particularly in regard to the staining reactions of Ewing's sarcoma and of sympathicoblastoma, in order to differentiate clearly these two forms of malignant growths.

The clinical histories of 12 cases of sympathicoblastoma are here reported (case 10 to case 21, inclusive).

CASE 10.—A white youth aged 16 complained of pain in the right arm present for six months and of pain in the left arm present for one week. Examination revealed weakness and hypoesthesia of both arms, tenderness in the cervicodorsal region and positive results from a Queckenstedt test. Roentgen examination in March 1933 was reported as showing no abnormalities. At operation in the same month an extradural nonencapsulated tumor extending from the fourth to the



seventh cervical vertebra was removed. The tumor had eroded the intervertebral foramen as it passed out into the neck. The condition of the patient improved after the operation, but symptoms of compression of the spinal cord again developed in the fall of 1935. Roentgen examination in November 1935 revealed increased density in the bodies of the seventh cervical and first thoracic vertebrae, with slight destructive changes and a slight periosteal reaction. There also appeared to be a mass anterior to the vertebral bodies which displaced the trachea forward. Roentgen examination in February (fig. 32) revealed an increase in the size of the prevertebral mass. Laminectomy was again performed in February, but no tumor was found. The patient's condition did not improve, and he died of tracheal obstruction in September. At autopsy a friable hemorrhagic tumor was found overlying the bodies of the cervical vertebrae. Though it was not encapsulated, it was fairly well circumscribed, almost polypoid in appearance. The vertebral bodies were eroded and invaded. The tumor extended into the spinal canal and compressed the spinal cord. It encircled the esophagus and the trachea and extended downward into the upper mediastinum. The subclavian and jugular veins



Fig. 32 (case 10).—Sympathicoblastoma in the cervical region. The roentgenogram shows increased density of the bodies of the seventh cervical and first thoracic vertebrae, with slight destructive changes in the anterior portions of the bodies of these vertebrae. A paravertebral mass is visible which has displaced the trachea anteriorly. A laminectomy has previously been done.

were invaded. The lungs contained metastatic nodules. Microscopic examination revealed a cellular tumor invading muscle and divided into large alveoli by fibrous septums. The cells were almost entirely sympathogonia. Necrotic areas, rare, poorly formed rosettes and occasional mitotic figures were present.

CASE 11.—A white woman aged 30 complained of pain in the back present for six months and of numbness of the legs and feet present for two weeks. On examination, tenderness was elicited over the sixth and seventh thoracic vertebrae and a partial spastic paralysis, with hypoesthesia, was present below the level of the seventh rib. Roentgen examination in December 1930 showed destruction and partial collapse of the body of the sixth thoracic vertebra and destruction of the spinous processes and the laminae of the thoracic vertebrae from the fifth to the seventh. At operation in the same month an extradural tumor was found destroying bone, pressing on the spinal cord and extending into the mediastinum.

The mass was partially removed. The patient's condition improved, but she returned in August 1931 complaining of pain in the back, radiating to the right breast, and of numbness of the fingers. Operation was again performed, but the tumor was inoperable. The patient received roentgen therapy postoperatively but died in November. Postmortem examination revealed a mass overlying the vertebral bodies from the fourth thoracic to the seventh. It had invaded and destroyed the body of the fifth thoracic vertebra. The spinal cord and the dura also had been invaded and the tumor had metastasized to the lungs. Microscopic examination revealed a cellular tumor composed mostly of sympathoblasts and divided by fibrous septums. Cytoplasmic processes were prominent. Occasional mitotic figures, poorly formed rosettes and clumps of sympathogonia with parallel nuclei were present.

CASE 12.—A white youth aged 15 had an encapsulated tumor removed in November 1928. It had compressed the spinal cord at the level of the second and third thoracic vertebrae and had extended into the mediastinum. It had also caused partial paralysis. Roentgen therapy was given after the operation, but the tumor recurred and was removed again in 1931. In June 1932 pain developed at the neural roots at the level of the third thoracic vertebra, and paralysis was present below this level. Roentgen examination at this time showed a mass immediately to the right of the spine at the level of the fourth thoracic vertebra. The patient was again operated on, and a tumor was found which pressed on the spinal cord and extended into the neck and the upper part of the mediastinum. This tumor was partially removed. The patient's condition did not improve, and he died in October 1932. At autopsy a paravertebral mass was found in the upper thoracic region which had metastasized to other vertebrae, to a rib, to the femur and to the hypophyseal region of the skull. Microscopic examination revealed a cellular tumor almost entirely composed of sympathogonia and divided by fibrous septums. Many clumps and balls of closely packed nuclei were present. The cytoplasm was scanty, and mitotic figures were rare.

CASE 13.—A white woman aged 23 complained of pain in the right hip, extending down the thigh, present since September 1932. Examination revealed anesthesia of the outer side of the right foot and a tender mass to the right of the fourth and fifth lumbar vertebrae. Roentgen examination in April 1933 showed a destructive lesion involving the upper part of the right side of the sacrum and the right side of the fifth lumbar vertebra. In November the mass was removed, and roentgen therapy was given postoperatively. The patient died in August 1934, and at autopsy a huge tumor was found which had destroyed the right side of the sacrum, the right ileum and the lower lumbar vertebrae and had metastasized to the thoracic vertebrae, the sternum and the lung. Microscopic examination revealed a tumor composed chiefly of sympathoblasts, with well marked cytoplasmic processes. There were occasional mitotic figures and poorly formed rosettes.

CASE 14.—A white man aged 42 complained of pain in the lumbar region present for five years, of difficult urination present for seven months and of paralysis of the left leg present for four months. Examination revealed tenderness in the upper lumbar region. Roentgen examination was reported to have produced negative results. The patient died in April 1923, and at autopsy a hemorrhagic osseous mass was found, which arose to the left of the first and second lumbar vertebrae. The tumor had destroyed bone in that region and had invaded and filled the spinal canal. Roentgen examination of the postmortem specimen showed an osteosclerotic process in the region of the spinal canal (fig. 27). Microscopic examination revealed adult ganglion cells scattered throughout the tissue. Reactive bone,

fibrosis and an occasional giant cell were present. Numerous fibrils were seen about some of the ganglion cells. Some of these cells were embedded in bone, and a few sympathoblasts were present. An occasional mitotic figure was seen (fig. 31).

CASE 15.—A white man aged 45 complained of pain in the lower part of the back following an injury five months before and of pain in the chest and bloody sputum present for one month. A tumor had been noticed in the left axilla for one month. Roentgen examination revealed destruction of the left transverse process and of the left side of the body of the fourth lumbar vertebra. There were also osteolytic changes in the ribs and in the skull. At autopsy in October 1931 a tumor of the left adrenal medulla was found, with metastases to the spine, the ribs, the skull, the brain, the lymph glands and the lungs. Microscopic examination showed a cellular tumor composed principally of sympathoblasts, divided by fibrous septums into alveoli. Most of the nuclei were elongated and lay parallel to each other in small groups. An occasional mitotic figure was found, as well as an occasional poorly formed rosette.

CASE 16.—A white man aged 29 complained of pain in the back following an injury eighteen months before and of gradually increasing symptoms of compression of the spinal cord ending in complete paralysis of both lower extremities three days before roentgen examination. There were sensory changes at the level of the eighth thoracic segment. Roentgen studies in September 1929 showed osteosclerosis of the body of the tenth thoracic vertebra, with a fusiform paravertebral mass (fig. 25). Laminectomy in the same month disclosed an extradural tumor adherent to the laminae of the ninth thoracic vertebra and pressing on the spinal cord. Roentgen therapy was employed postoperatively. The condition of the patient was improved by the operation. In June 1930 a hard mass above the left clavicle was noted, which seemed to be attached to the spine. Roentgen examination at this time revealed osteosclerosis of the body of the sixth cervical vertebra. The patient died in April 1933. Permission for autopsy was not obtained. Microscopic examination revealed a cellular tumor composed almost entirely of sympathoblasts and divided by numerous fibrous septums. The nuclei were large and vesicular, with large nucleoli. The cytoplasm, though not abundant, was well marked and extended into short processes. There were present a few groups of sympathogonia with parallel nuclei. No rosettes were seen. Mitotic figures were rare.

CASE 17.—A white woman aged 17 complained of pain in the left leg present for five months and of weakness of the left leg, numbness of the left buttock and difficult urination present for six weeks. The fifth lumbar vertebra was tender, and there was a mass over the dorsum of the sacrum. Roentgen examination in April 1931 showed destruction of the laminae and transverse processes of the left sacral vertebrae from the second to the fifth. At operation in the same month an extradural tumor was found in the sacral canal which extended into the lumbar canal and out through the anterior sacral foramen. It was partially removed, and irradiation was given postoperatively. The patient was well in 1938, without recurrence of the symptoms. Microscopic examination revealed a cellular tumor invading muscle. Both sympathogonia and sympathoblasts were present. Cytoplasmic fibrils were present in abundance. Groups of deeply staining, elongated, parallel nuclei were frequent. No well formed rosettes were seen, and mitotic figures were rare.

CASE 18.—A white man aged 47 complained of loss of control of the bladder present for eight months, numbness of the feet present for two months and difficult

walking present for one month. On examination, partial paralysis, with hyposthesia of the lower extremities, and positive results of a Queckenstedt test were found. Roentgen examination was reported as showing "hypertrophic arthritis" (plates not available). In December 1924 an intradural nonencapsulated tumor extending from the eleventh thoracic vertebra to the third lumbar vertebra was partially removed. The lamina of the first lumbar vertebra was perforated by an irregular opening, and the neighboring laminae were thin and soft. The patient was discharged with his condition improved. Follow-up was not possible. Microscopic examination revealed a cellular tumor divided by fibrous septums. Sympathoblasts predominated in number over sympathogonia. Cytoplasmic processes were well marked and formed a network of fibrils. A few groups of parallel, hyperchromatic, elongated nuclei were seen. Mitotic figures were rare (fig. 29).

CASE 19.—A white woman aged 45 complained of pain in the back and at the roots of the spinal nerves present for four weeks and of increasing symptoms of compression of the spinal cord present for three weeks. The third and fourth thoracic vertebrae were tender, and there were sensory changes at the level of the sixth thoracic segment. No roentgenogram was taken. In October 1936 a nonencapsulated extradural tumor was removed. This tumor had pressed on the spinal cord and had extended into the mediastinum through a defect in the bony column at the level of the third and fourth thoracic vertebrae. The patient's condition was slightly improved in April 1937. Microscopic examination revealed a cellular tumor composed mainly of sympathogonia. A few poorly formed rosettes were seen. In some areas there were groups of elongated, hyperchromatic, closely packed nuclei lying parallel to one another. These groups sometimes formed balls or whorls of nuclei. Mitotic figures were rare (fig. 28).

CASE 20.—A man aged 24 complained of pain over the sacrum present for five months, followed by pain in the legs and numbness of the right foot. Roentgenoscopic examination showed a destructive lesion in the body of the fifth lumbar vertebra, without collapse, and destruction of the right transverse process. The patient died in June 1930. Microscopic examination (it is not known whether the tissue was obtained at operation or at autopsy) revealed a cellular tumor invading muscle. Sympathoblasts were present in excess. A network of fibrils was a prominent feature. No well formed rosettes were seen, but clumps of sympathogonia were present. Mitotic figures were scarce.

CASE 21.—A white woman aged 66 complained of pain in the lower part of the back present for one and one-half years. There was tenderness in the lumbosacral region. Roentgen examination in January 1937 showed destruction of the left transverse process and pedicle of the third lumbar vertebra and a paravertebral mass in that region, with an irregular bony shell (fig. 26). A biopsy was performed in the same month. Microscopic examination revealed a cellular tumor composed mostly of sympathoblasts. Large necrotic areas were present. Mitotic figures were rare (fig. 30).

#### GLIAL AND SHEATH TUMORS OF THE SPINAL CORD

Glial tumors and tumors of the neural sheath and of the meninges may in some cases be difficult to distinguish preoperatively from other neoplastic lesions of the spine. It has already been shown in the preceding discussion that some of the primary or paravertebral tumors of the spine may cause neurologic symptoms as the first and only complaint. As a rule, however, intramedullary tumors and benign tumors of the

nerve sheaths may be diagnosed by the fact that the neurologic features are prominent and that the changes in bone, if present, are either slight or characteristic. This does not apply to malignant tumors of this type or to certain varieties of glial tumors. The latter tumors are uncommon.

*Perineurial Fibroblastoma (Neurinoma).*—This tumor occurs in the spine with a frequency approximately equal to that of meningeal tumors, and each is more common in this region than is glioma. Perineurial fibroblastoma (neurinoma) occurs more frequently in the lumbar and the sacral region than in other parts of the spine. The benign form is a firm, encapsulated intradural or extradural tumor attached to a nerve root. It may or may not extend outside the spinal canal in hour-glass fashion. It produces symptoms of compression of the spinal cord or of the cauda equina, often associated with pain at the nerve roots. Even when changes in bone occur, pain in the back is not a common complaint, though localized tenderness may be present. Camp, Adson and Shugrue pointed out that this tumor more commonly than any other glial or nerve sheath tumor produces changes in the vertebral column. According to their studies, the pedicle, the laminae and the body of the vertebra are eroded in the order mentioned. The transverse process may be eroded by an extraspinal portion of the tumor. Figure 33 shows erosion of the pedicles and laminae of the fifth lumbar vertebra. A lateral view in this case showed a circular defect 3 cm. in diameter at the right intervertebral foramen. The erosion caused by these benign tumors is smooth and must be distinguished from the destruction of bone produced by invasive tumors. Slight erosions are easily overlooked. Measurement of the spinal canal reveals changes in bone in a large number of the cases. Basing their studies on a series of tumors of the spinal cord, Elsberg and Dyke<sup>33</sup> were able by this method to detect changes in 42 per cent of 67 cases and in 70 per cent of 20 cases in which the tumors were between the tenth thoracic vertebra and the first sacral vertebra. A neurinoma may occasionally contain calcified areas which are visible in the roentgenogram, but this feature is much more characteristic of meningiomas.

In this series there were 8 benign neurinomas which produced changes in bone detected in the roentgenogram or at operation. No attempt was made with these or with any of the glial or nerve sheath tumors to detect slight changes by measurement of the spinal canal.

Sarcoma of a nerve sheath is not so clearly characteristic in the roentgenogram as is neurinoma. There were 4 such tumors in this

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33. Elsberg, C. A., and Dyke, C. G.: *Diagnosis and Localization of Tumors of the Spinal Cord by Means of Measurements Made on the X-Ray Films of the Vertebrae, and the Correlation of Clinical and X-Ray Findings*, Bull. Neurol. Inst. New York 3:359, 1934.

series, and in 2 of the cases pain in the back was a prominent complaint and preceded the symptoms of compression of the spinal cord. Destruction of bone, rather than smooth erosion, was produced in every case (fig. 34). Sarcoma of a nerve sheath is more common than meningeal sarcoma.

*Meningeal Tumors.*—Meningeal tumors occur more frequently in the thoracic and the cervical region than in other portions of the spine. The benign form is a firm, encapsulated intradural or extradural tumor attached to the meninges. It may occasionally have an extraspinal portion.

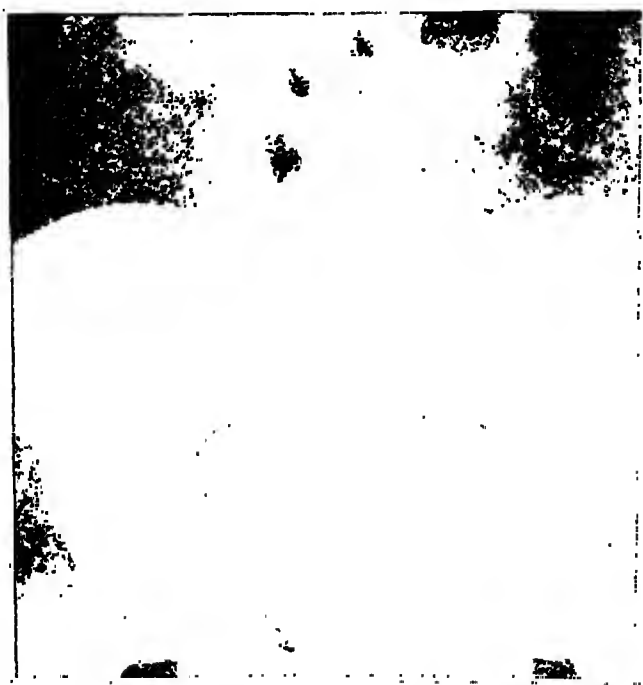


Fig. 33.—Perineurial fibroblastoma at the level of the fifth lumbar vertebra. The roentgenogram shows erosion of the laminae and of both pedicles of the fifth lumbar vertebrae, most marked on the right side. (Case of Dr. W. McL. Shaw, Jacksonville, Fla.)

There were 6 meningiomas in this series which were detectable in the roentgenogram by reason of gross changes in bone or calcification of the tumor. Pain in the back was not a feature. Erosion of bone is less commonly produced than it is by neurinoma. The benign tumors cause a smooth erosion of bone. Calcification, even ossification, is not uncommonly found with these tumors and may be present in sufficient amounts to show in the roentgenogram (fig. 35). Sarcoma of the



Fig. 34.—Sarcoma of the neural sheath involving a thoracic vertebra. The roentgenogram shows destruction, with partial collapse, of the body of the eighth thoracic vertebra. (Case of Dr. E. T. Wentworth, Rochester, N. Y.)



Fig. 35.—Meningeal fibroblastoma. The roentgenogram shows a calcified mass lateral to the fourth cervical vertebra which has destroyed the pedicle and transverse process in this region. (Case of Dr. A. Wilson Smith, Chicago.)

meninges causes an invasive type of destruction of bone. There was 1 such tumor in this series.

*Multiple Neurofibromatosis.*—In this neoplastic condition neurofibromas may form on all the spinal nerve roots and cause erosion of bone in the region of the intervertebral foramina (fig. 36). A paravertebral mass may be visible in the roentgenogram, together with underlying destructive changes in the bone. There were 2 cases of this condition.

*Glial Tumors.*—Intramedullary glioma is less common than nerve sheath tumor in the spine and rarely produces gross changes in bone.



Fig. 36.—Multiple neurofibromatosis. The roentgenogram shows a faint, well circumscribed lobulated mass in the left paravertebral region. Several of the pedicles of the thoracic vertebrae in this region are seen to be absent or eroded.

There were but 2 such intramedullary gliomas in this series. One caused a smooth erosion of the laminae, and the other was demonstrable in the roentgenogram because of calcification in the tumor itself.

There were 6 extramedullary glial tumors in this series which caused osseous changes. All these tumors may be classed as primitive, and all occurred below the level of the eleventh thoracic vertebra. There were 3 ependymomas. These tumors caused a smooth erosion of bone. There were 2 heterotopic astroblastomas (possibly unusual varieties of ependymoma), 1 of which caused an erosion of the laminae and the



other of which invaded and destroyed bone (fig. 37). The remaining tumor was a primitive neuroepithelioma (fig. 38) which occurred ventral to the sacrum, causing destruction of that bone.

In general, it may be said that the glial tumors which cause osseous changes are of the less differentiated, extramedullary type and that they occur in the lumbar and sacral regions.

#### TERATOID AND TERATOLOGIC TUMORS

Sacrococcygeal tumors are often grouped together. Ependymoma, chordoma, neuroepithelioma and giant cell tumor are sometimes described

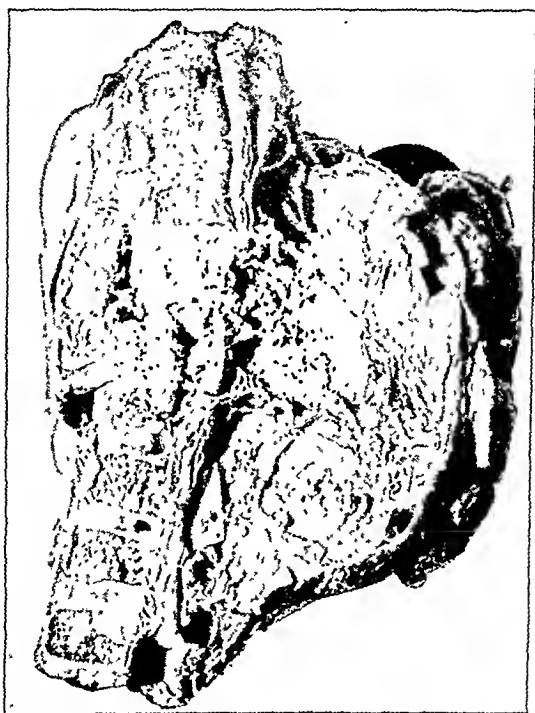


Fig. 37.—Astroblastoma in the dorsolumbar region. The photograph shows a longitudinal section of the lesion at autopsy. There is a large paravertebral mass dorsal to the spine and a smaller ventral mass. Six vertebrae are either partially or completely destroyed. At postmortem examination the spinal cord could be traced as a slender fibrous cord traversing the mass. (Case of Dr. Horace B. Davidson, Columbus, Ohio.)

under this heading. We have mentioned these tumors elsewhere. The dorsal tumors are usually dermoid cysts or teratomas. Giant cell tumor and ependymoma usually occur within the body of the sacrum. Ventral tumors are numerous and varied. Teratoma and chordoma are common in this region.

In this series there were 2 dorsal tumors, 1 an intraspinal dermoid cyst and the other an intraspinal teratoma. One occurred in the lower thoracic region, and the other in the upper lumbar region. Both tumors compressed the spinal cord, and both were associated with hairy moles on the skin surface. One patient was 3 years of age, and the other, 35.

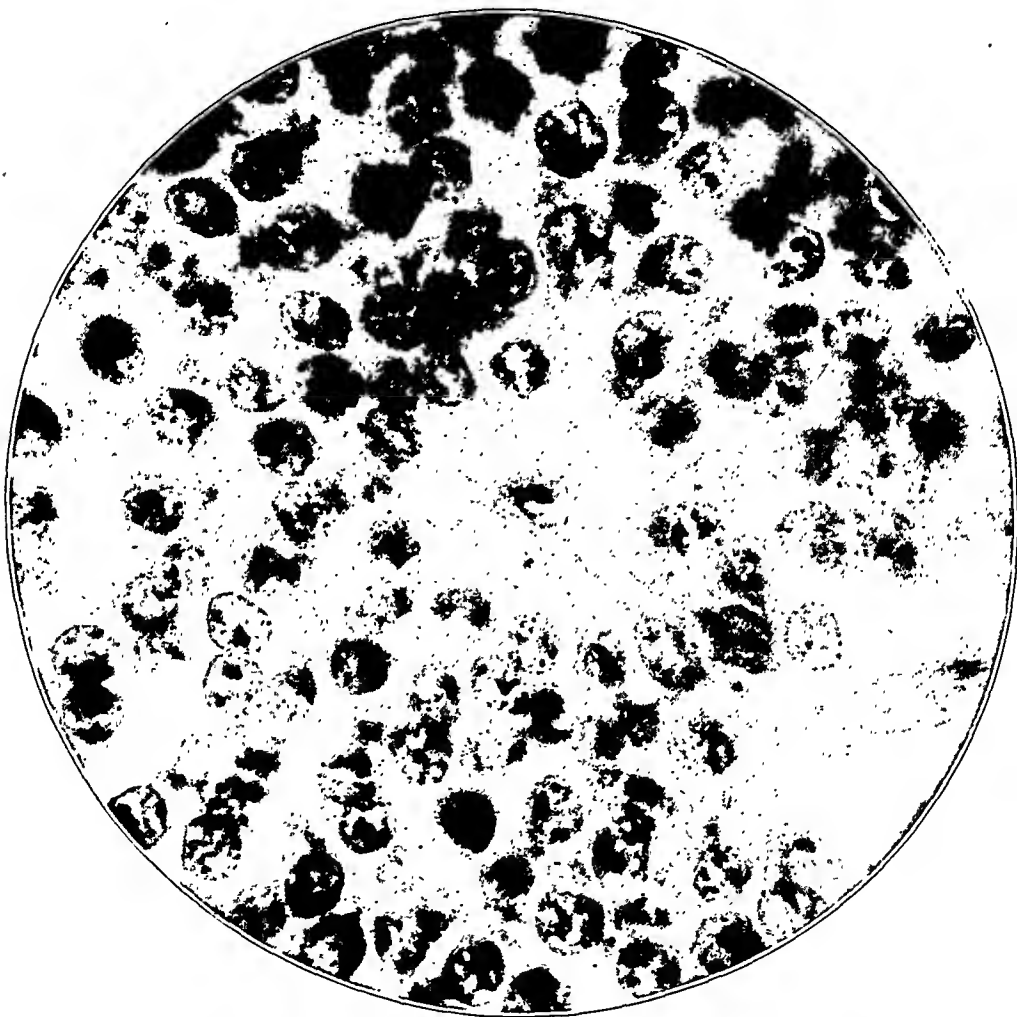


Fig. 38.—High power (oil immersion) photomicrograph of a neuroepithelioma, showing rosette formation, with well marked radiating cytoplasmic processes. (Case of Dr. Carleton B. Peirce, Ann Arbor, Mich.)

There were 3 ventral tumors in this series. One was a primitive neuroepithelioma, which has already been described with the glial tumors. The other 2 were teratomas in which all three of the primitive germ layers were present. Nerve tissue elements were present in both of these tumors. Both patients were infants, 1 of whom died soon after delivery and the other at 8 months of age.

## DIFFERENTIAL DIAGNOSIS

Spinal tumor is frequently diagnosed as tuberculosis of the spine. It may be impossible to differentiate the one from the other by roentgen examination. This is true particularly in regard to the malignant tumors. Certain points, however, may be of use. Fray has pointed out that a vertebral body destroyed by malignant disease is apt to collapse uniformly, producing an "accordion effect." A triangular compression of a vertebral body is more common in tuberculosis. This variation in the type of collapse accounts for the fact that a gibbus is usually less marked in a neoplastic lesion than in a tuberculous lesion. A firm type of tumor, of course, may destroy a vertebral body and yet prevent any appreciable collapse. A characteristic of tuberculosis is destruction in the anterior portion of adjoining vertebral bodies, a very uncommon finding with spinal tumor. Compere and Garrison<sup>34</sup> stated that they have never seen *tuberculosis primarily affect the neural arch or its appendages*. These parts are frequent sites of neoplastic growth. Tuberculosis shows little tendency to regeneration of bone (Compere and Garrison), a marked feature with some tumors, especially after irradiation. A paravertebral shadow when it is not distinctive of some particular type of tumor is of no diagnostic value. The presence or absence of the intervertebral disk is likewise of little help. In some cases it may be found necessary to attempt an aspiration to obtain material for culture or for microscopic examination. In general, however, it may be said that in the absence of compression of the spinal cord, which is a symptom requiring operative relief, it is best to treat the doubtful condition by rest and by irradiation.

Pyogenic osteomyelitis of the spine should not, as a rule, be confused with neoplasm. The history of a preceding infection, the acute febrile state and the early destruction of the intervertebral disk should establish the diagnosis. Acute osteomyelitis of the spine is uncommon compared with tuberculosis.

The lesions of the spine which also must be borne in mind are those of typhoid fever, of syphilis, of fungous infection and of osteomalacia.

In any case of lesion of the spine in which the diagnosis is doubtful it is well to make a roentgen examination of the entire skeleton. The possibility of the presence of syphilis may be ruled out by serologic tests or by the response to specific therapy. The urine should be examined for Bence Jones bodies. The response to roentgen therapy may be helpful in the diagnosis.

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34. Compere, E. L., and Garrison, M.: Correlation of Pathologic and Roentgenologic Findings in Tuberculosis and Pyogenic Infections of the Vertebrae: Fate of the Intervertebral Disk, *Ann. Surg.* **104**:1038, 1936.

## SUMMARY

Metastatic carcinoma, usually from the breast or from the prostate, is the most common neoplastic condition of the vertebral column. Cancer of the breast may involve any region of the spine; the lesions are usually multiple and destructive. Carcinoma of the prostate involves the sacro-lumbar region and produces sclerosis of bone. These multiple lesions of the spine in adults must be differentiated from multiple myeloma, which produces multiple circular defects with a tendency to pathologic fracture and collapse. Involvement of the spine in Hodgkin's disease, lymphosarcoma and leukemia may simulate metastatic carcinoma.

Benign giant cell tumor and osteochondroma are the most common benign tumors of the spine. Giant cell tumor usually affects the spine of the young adult below the cervical region, tends to involve the neural arches and produces a trabeculated lesion outside the body of the vertebra. The healing phase of this condition produces bone cysts, which may also complicate Recklinghausen's disease associated with parathyroidism and demineralization of the entire spine. Osteochondroma may occur in any portion of the spine. The neural arches are affected by an osseous growth, with a clearly demarcated osseous shadow visible in the roentgenogram. Hemangioma of the vertebra is rare and produces characteristic vertical striations or well ordered radiating spicules of bone without collapse of the body of the vertebra.

Osteogenic sarcoma of the spine, including chondrosarcoma, osteolytic sarcoma and sclerosing sarcoma, may be secondary to multiple exostoses or to Paget's disease. These sarcomas show a wide age distribution. Chondrosarcoma of the spine tends to involve several vertebrae and produces characteristic calcified paravertebral shadows. The roentgenogram in a case of sclerosing sarcoma shows irregular formation of new bone in the soft parts. Osteolytic sarcoma is less characteristic in the roentgenogram and produces a rapidly extending region of osseous destruction, with infiltration of the soft parts. Chordoma affects either the spheno-occipital or the sacrococcygeal region of the spine of the adult and produces a bone-destructive lesion, which increases gradually over a period of months or years.

Twelve undifferentiated neuroblastic tumors—sympathicoblastomas—involved the spine in the present series. Such a tumor is usually situated in the lower part of the thoracic or in the lumbar region. It destroys bone and produces a paravertebral shadow. It tends to metastasize to the regional lymph nodes and to other bones and on microscopic examination is often mistaken for Ewing's sarcoma. Like Ewing's sarcoma it responds to irradiation. No typical Ewing sarcoma of the spine was found in the present series, and the tumors previously classed as such were thought on further study to be sympathicoblastomas.

A glial or nerve sheath tumor of the spinal cord may involve the vertebral column. A meningeal tumor usually affects the thoracic or the cervical region and may be visible in the roentgenogram, either because of erosion of bone or because of calcification in the tumor. Neurinoma or neurofibroma of a spinal nerve root more often causes erosion of bone than does a meningeal tumor. Neurinoma is most common in the lumbar and the sacral regions. This benign tumor attached to a nerve root may slowly erode bone, the pedicle, the laminae and the body of the vertebrae being affected in the order mentioned. Erosion is more rapid and more pronounced with a malignant nerve sheath tumor affecting the roots of the spinal nerves. Glial tumors producing changes in bone are rare. They are usually primitive neuroepitheliomas or ependymomas. In the sacrococcygeal region a benign or malignant teratoma may erode bone.



*Periosteal Regeneration.*—According to Duhamel,<sup>4</sup> Syme,<sup>5</sup> Ollier,<sup>6</sup> Axhausen,<sup>7</sup> Haas,<sup>8</sup> Mayer and Wehner,<sup>9</sup> Phemister,<sup>10</sup> Berg and Thalhimer,<sup>11</sup> Rohde,<sup>12</sup> Blaisdell and Cowan,<sup>13</sup> Mock,<sup>14</sup> Ham,<sup>15</sup> Smith,<sup>16</sup> Haldeman,<sup>17</sup> Leadbetter,<sup>18</sup> Riess,<sup>19</sup> Schepelmann,<sup>20</sup> Bisgard<sup>21</sup> and many others, periosteum and endosteum are definite organs for the formation and repair of bone. Osteoblasts, according to this theory, never come from adult bone cells, but arise from the cells of the periosteum and, to a lesser extent, from the endosteum.

*Osteoblastic Regeneration.*—Goodsir,<sup>22</sup> Macewen,<sup>23</sup> Brown and Brown,<sup>24</sup> Moore and Corbett,<sup>25</sup> Davis and Hunnicutt,<sup>26</sup> Gallie and

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9. Mayer, L., and Wehner, E.: *Experimental Study of Osteogenesis*, Am. J. Orthop. Surg. **12**:213-244, 1914.

10. Phemister, D. B.: *Fate of Transplanted Bone and the Regenerative Power of Various Constituents*, Surg., Gynec. & Obst. **18**:303-333, 1914.

11. Berg, A. A., and Thalhimer, W.: *Regeneration of Bone*, Ann. Surg. **67**:331-347, 1918.

12. Rohde, C.: *Does Bone Form from Osteoblasts or from Metaplasia of Surrounding Connective Tissue?* Surg., Gynec. & Obst. **41**:740-772, 1925.

13. Blaisdell, F. E., and Cowan, J. F.: *Healing of Simple Fractures*, Arch. Surg. **12**:619-654 (March) 1926.

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15. Ham, A. W.: *Histological Study of Early Phases of Bone Regeneration*, J. Bone & Joint Surg. **12**:827-844, 1930.

16. Smith, F. D.: *Periosteal Regeneration of Bone*, Surg., Gynec. & Obst. **20**:547-552, 1915.

17. Haldeman, K. O.: *Role of Periosteum in Healing of Fractures*, Arch. Surg. **24**:440-450 (April) 1932.

18. Leadbetter, G. W.: *Periosteum*, Arch. Surg. **22**:754-785 (May) 1931.

19. Riess, E.: *Experimentelle Studien über die knochenbildende Kraft des Periostes*, Arch. f. klin. Chir. **129**:750-757, 1924.

20. Schepelmann, E.: *Freie Periostverpflanzung*, Arch. f. klin. Chir. **101**:499-510, 1913.

21. Bisgard, J. D.: *Experimental Studies of Reparative Costal Chondrogenesis and of Transplanted Bone*, Surg., Gynec. & Obst. **58**:817-822, 1934.

22. Goodsir, J.: *Anatomical Memoirs of John Goodsir*, edited by William Turner, Edinburgh, A. & C. Black, 1868, vol. 2.

23. Macewen, W.: *Growth of Bone*, Glasgow, J. Macle hose & Sons, 1912.

Robertson,<sup>27</sup> Cohn and Mann,<sup>28</sup> Ely,<sup>29</sup> Keith,<sup>30</sup> Sever,<sup>31</sup> Jaffe<sup>32</sup> and others have stated that periosteum serves simply as a limiting membrane and a convenient source of blood supply, but plays no active role in osteogenesis. These physicians have upheld one of the two following opinions: (1) After injury bone cells are liberated from their lacunas, and these multiply to form new bone; (2) after injury wandering connective tissue cells are drawn to the site of reaction and through their pluripotentiality become osteoblasts.

*Extracellular Deposition of Calcium Salts.*—This theory, advocated by Bancroft,<sup>33</sup> Leriche and Policard,<sup>34</sup> Asami and Dock,<sup>35</sup> Neuhoof,<sup>36</sup> Huggins,<sup>37</sup> Roome and McMaster,<sup>38</sup> Petrow,<sup>39</sup> Murray<sup>40</sup> and others, stated that there is no definite bone-producing cell but that after injury calcium salts are laid down in the framework of the adjacent connective tissue by chemotaxis. These connective tissue cells then become bone cells by metaplasia, or by functional adaptation.

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25. Moore, J. E., and Corbett, J. F.: Studies on the Function of Periosteum, Surg., Gynec. & Obst. **19**:5-9, 1914.

26. Davis, J. S., and Hunnicutt, L. A.: Osteogenic Power of Periosteum, Ann. Surg. **61**:672-685, 1915.

27. Gallie, W. E., and Robertson, D. E.: Repair of Bone, Brit. J. Surg. **7**:211-261, 1919.

28. Cohn, I., and Mann, G.: Further Study of Bone Repair, South. M. J. **9**:235-250, 1916.

29. Ely, L. W.: Study of Buried Bone, Ann. Surg. **70**:747-749, 1919.

30. Keith, A.: Growth and Regeneration of Bone, Brit. J. Surg. **5**:685-693, 1918; **6**:19-23 and 160-165, 1918.

31. Sever, J. W.: Nonunion in Fracture of the Shaft of the Humerus, J. A. M. A. **104**:382-386 (Feb. 2) 1935.

32. Jaffe, H. L.: Structure of Bone: Wolff's Law, Arch. Surg. **19**:24-52 (July) 1929.

33. Bancroft, F. W.: Bone Repair Following Injury and Infection, Arch. Surg. **5**:646-677 (Nov.) 1922.

34. Leriche, R., and Policard, A.: Le périoste et son rôle dans la formation de l'os, Presse méd. **26**:143, 1918.

35. Asami, G., and Dock, W.: Experimental Studies on Heteroplastic Bone Formation, J. Exper. Med. **32**:745-666, 1920.

36. Neuhoof, H.: Fascial Transplantation into Visceral Defects, Surg., Gynec. & Obst. **24**:383-427, 1917.

37. Huggins, C. B.; McCarroll, H. R., and Blocksom, B. H.: Experiments on the Theory of Osteogenesis; Influence of Local Calcium Deposits on Ossification; Osteogenic Stimulus of Epithelium, Arch. Surg. **32**:915-931 (June) 1936.

38. Roome, N. W., and McMaster, P. E.: Influence of Venous Stasis on Heterotopic Formation of Bone, Arch. Surg. **29**:54-58 (July) 1934.

39. Petrow, N. N.: Zur Frage nach der Quelle der Regeneration bei Knochen-überpflanzung, Arch. f. klin. Chir. **105**:915-923, 1914.

40. Murray, C. R.: Repair of Fractures, Minnesota Med. **13**:137-152, 1930.



## TRANSPLANTATION OF BONE

Investigators have differed in their opinions concerning the fate of autoplasmic bone grafts, according to the theory of osteogenesis they have supported. Those who have concluded that bone in itself is osteogenic have interpreted their results to show that bone grafts grow; those who have concluded that periosteum is the source of new bone have stated that bone grafts die and are absorbed or may act as a framework for new bone, and those who have been convinced that connective tissue forms new bone have stated that the graft acts as a source of calcium salts, which stimulates metaplasia in the connective tissue.

Macewen was able to show phenomenal results in his experiments. Free grafts of bone grew, chips of bone produced new bone and chips implanted into muscle tissue produced large plaques of new bone. Phemister, Haas,<sup>41</sup> Axhausen, Thalheimer and Brooks<sup>42</sup> have published work which seems to show that free transplants of bone act as a source of regeneration and are not merely a trellis into which new bone grows from neighboring sources.

McWilliams,<sup>43</sup> Phemister, Rohde, Ham, Pollack<sup>44</sup> and others have adopted the very reasonable view that the success or failure of a graft of bone or periosteum, or both, depends on the rapidity with which the graft is able to establish a new and adequate blood supply. According to this view, small bone grafts do not need a periosteal covering because they easily become vascularized, whereas larger grafts may fail because of a lack of this vascularity. Periosteum on these larger grafts may insure success because of the preformed vascular channels present.

Brooks and Hudson, using dogs, obtained success with 84 per cent of autoplasmic grafts of the ulna, as compared with success with 76 per cent of homoplasmic grafts in the same region. They concluded that the compatibility of tissues is an important factor in the success of these grafts. They used intravital staining to demonstrate the formation of new bone.

Camitz, Holmgren and Johansson<sup>45</sup> were successful with homologous transplants in dogs and found that all elements of the graft were concerned in healing and in the regeneration of bone.

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41. Haas, S. L.: Regeneration of Bone and Cartilage at the Costochondral Junction, *Surg., Gynec. & Obst.* **19**:604-617, 1914.

42. Brooks, B., and Hudson, W. A.: Studies on Bone Transplantation, *Arch. Surg.* **1**:284-309 (Sept.) 1920.

43. McWilliams, C. A.: Periosteum in Bone Transplantation, *Surg., Gynec. & Obst.* **18**:159-169, 1914.

44. Pollack, W. E.; McKenney, P. W., and Blaisdell, F. E.: Viability of Transplanted Bone, *Arch. Surg.* **18**:607-623 (Feb.) 1929.

45. Camitz, H.; Holmgren, H., and Johansson, H.: Study of Bone Transplants, *Acta chir. Scandinav.* **75**:1-67, 1934.

Gill<sup>46</sup> showed that autogenous transplantation of entire metatarsal bones in a dog's paws was accompanied by moderate success. He also cited many clinical instances (Lexer) of homoplastic transplantation of fingers, toes, half joints and even, in a few instances, entire knee joints.

#### REGENERATION OF BONE

Ely,<sup>47</sup> in studying the healing of fractures in cats, became convinced that the periosteum served only as a container for the reparative callus, acting also in the capacity of a splint. Gallie and Robertson also stated that periosteum has no osteogenic function, serving merely as a convenient source of blood supply. Macewen expressed the opinion that periosteum by pressure on the osteoblastic mass serves to limit the amount of callus formed.

On the other hand, Haldeman found periosteum to be the chief factor in the healing of fractures. He stated that endosteal callus aids, but that in the absence of periosteum it is often incapable of causing, complete union. He found that the interposition of periosteum between the fractural fragments caused nonunion, because new bone did not tend to bridge the defect in the absence of periosteum.

Various investigators have obtained new bone formation after subcutaneous injection of emulsions of periosteal cells. Carrel<sup>48</sup> and others have found that periosteum retains its osteogenic properties even after having been placed in cold storage for several days before implantation. Recently, Bisgard<sup>49</sup> has implanted periosteal and osseous grafts into the anterior chamber of the eye of the rabbit, with and without the addition of calcium salts. This is essentially a tissue culture method, and he found that both types of graft are osteogenic. The addition of bone ash or bone salts made no change in the results, nor would the fascia ossify even in the presence of ash or bone salts.

#### HETEROTOPIC FORMATION OF BONE

It has been known for a long time that true bone may form in healing epigastric wounds, in occluded ureters and renal pelves and in fascial grafts used in repairing defects in the urinary bladder. Keith<sup>50</sup>

46. Gill, A. B.: Transplantation of Entire Bones and Their Joint Surfaces, *Ann. Surg.* **61**:658-671, 1915.

47. Ely, L. W.: Experimental Study in Healing of Fractures, *Arch. Surg.* **5**:527-560 (Nov.) 1922.

48. Carrel, A.: Preservation of Tissue and Its Applications in Surgery, *J. A. M. A.* **59**:523-527 (Aug. 17) 1912.

49. Bisgard, J. D.: Ossification: Influence of the Mineral Constituents of Bone, *Arch. Surg.* **33**:926-939 (Dec.) 1936.

50. Keith, A.: Origin and Nature of Osteoblasts, *Proc. Roy. Soc. Med.* **21**: 301-308, 1927.

discussed these observations and felt that the phenomena could be explained only by the hypothesis of Leriche, that bone is formed in the presence of reacting connective tissue and of excess calcium salts. Asami and Dock had previously studied heterotopic formation of bone in the urinary tract, stating that new bone is formed by metaplasia of fixed connective tissue cells. Neuhof, in his extensive work with fascial transplants, found that there was early disintegration followed by replacement with firm fibrous tissue. Bone frequently was formed, especially in the bladder. He also explained this osteogenesis on the basis of metaplasia in the connective tissue. Huggins<sup>51</sup> concurred in the observations of the effect on the formation of bone when bladder mucosa was transplanted into connective tissue. He found that bladder mucosa normally secretes calcium and phosphorus, and he indorsed the theory of Leriche. Roome and McMaster<sup>52</sup> found that venous stasis favored the laying down of heterotopic bone. They further observed that this new bone tended to be absorbed subsequently. This coincides with the theory of Wolff<sup>52</sup> which stated that bone is anatomically adapted to its function, and with the idea of Roux,<sup>53</sup> which is that functionless bone is absorbed.

#### CHEMICAL INHIBITION OF RIB REGENERATION

Head,<sup>54</sup> in 1927, was the first to advocate the use of chemical inhibition of rib regeneration in thoracic surgery as an aid to collapse, exposure and drainage. In an experimental series he used a stick of silver nitrate, a 50 per cent solution of silver nitrate, concentrated chromic acid and Zenker's solution. He found that silver nitrate gave extensive necrosis with a high incidence of pleural perforation and death. Chromic acid gave satisfactory inhibition of regeneration for four weeks, and Zenker's solution, for six weeks. It is interesting to note that Head stated that chemical inhibition of rib regeneration is contraindicated in cases of extrapleural thoracoplasty for surgical collapse in pulmonary tuberculosis. He based this statement on the assumption that since the mediastinum is not fixed, permanent mobilization of the chest wall would produce paradoxical respiration in the collapsed lung, with a consequent reduction in the already compromised vital capacity.

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51. Huggins, C. B.: Formation of Bone Under the Influence of Epithelium of the Urinary Tract, *Arch. Surg.* **22**:377-408 (March) 1931.

52. Wolff, J.: *Das Gesetz der Transformation der Knochen*, Berlin, A. Hirschwald, 1892.

53. Roux, W.: *Die Entwicklungsmechanik, ein neuer Zweig der biologischen Wissenschaft*, in *Vorträge und Aufsätze über Entwicklungsmechanik*, Leipzig, Wilhelm Engelmann, 1905, vol. 1, pp. 1-283.

54. Head, J. R.: Prevention of Regeneration of the Ribs, *Arch. Surg.* **14**:1209-1215 (June) 1927.

Meiss<sup>55</sup> in 1930 noticed that regeneration of the ribs hindered collapse in successive stages of thoracoplasty. In dogs, he resected ribs and applied Dakin's solution of formaldehyde U. S. P. diluted 1:10, chromic acid and Zenker's solution to the periosteal beds. Solution of formaldehyde was found to give inhibition of regeneration for at least three months and was superior to the other agents used because it did not cause pleural perforations. Meiss advocated the application of solution of formaldehyde to the periosteal beds after rib resection to facilitate the later stages of thoracoplasty, to allow longer periods between stages and to facilitate an intrathoracic operation if one is needed subsequently.

In 1930 Torraca<sup>56</sup> treated the periosteal beds with thermocautery, phenol, solution of formaldehyde, Bouin's solution, alcohol and silver nitrate. All of these except silver nitrate gave inhibition of regeneration, but the application of most of them was accompanied by perforation and death. Solution of formaldehyde was found to be the most satisfactory and gave the lowest incidence of pleuropulmonary adhesions. Zenker's solution has been successfully used by Trout<sup>57</sup> for inhibition of rib regeneration in thoracoplasties.

The first report of the extensive clinical use of the chemical inhibition of rib regeneration is that of Van Allen<sup>58</sup> in 1933. He stated that this procedure could be used to advantage not only in thoracoplasties but in graded operations for chronic empyema and bronchiectasis, in cardiolysis to insure permanent pliability of the precordium and in rib resections for acute empyema, abscess of the lung or cautery pneumonectomy. Van Allen<sup>58</sup> reported 40 cases of various types and could see no disadvantage in the use of solution of formaldehyde (U. S. P., diluted 1 to 10). He found that Zenker's solution gave inhibition for a shorter period and allowed fragmentary regeneration.

In the following year, Jachia<sup>59</sup> reported good results from the use of Zenker's solution for inhibition in cases requiring multiple stage thoracoplasty.

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55. Meiss, W.: Experimenteller Beitrag zur Vereinfachung der Thorakoplastik in mehreren Tempi, *Zentralbl. f. Chir.* **57**:349-354, 1930.

56. Torraca, L.: Ricerche sperimentali sui mezzi apti ad impedire la rigenerazione ossea dopo l'asportazione sottoperiosteale delle costole, *Clin. chir.* **6**:1433-1452, 1930.

57. Trout, H.: Release of Pericardial Adhesions, *Arch. Surg.* **23**:966-995 (Dec.) 1931.

58. Van Allen, C. M.: Chemical Treatment of Periosteum in Thoracoplasty to Inhibit Rib Regeneration, *Ann. Surg.* **97**:368-373, 1933.

59. Jachia, A.: Chemical Destruction of Periosteum in Treatment of Chronic Empyema, *J. Thoracic Surg.* **3**:623-633, 1934.

Haight <sup>60</sup> in 1936 stated that as a matter of routine he applies solution of formaldehyde U. S. P. diluted 1 to 10 to the periosteal beds and is thereby able to lengthen the interval between the stages of thoracoplasty. He concluded that collapse is improved and subsequent stages are facilitated.

#### RIBS OVERLYING EMPYEMA CAVITIES

Bisgard <sup>61</sup> in 1933 called attention to the fact that the external form of ribs overlying empyema cavities is changed, and that there is new bone formation along the inferior and internal aspect of these ribs. He noted this change even in acute empyema and concluded that these changes could be utilized as a means of estimating the size of empyema cavities by roentgenograms. He explained this proliferation of bone on the assumption that the infected pleura causes periostitis, which stimulates osteogenesis, and stated that the successive layers of new bone indicate a series of such stimuli. Bisgard <sup>61</sup> invoked Wolff's law of functional adaptation to explain the change in contour of the ribs, believing that the centripetal pull of the contracting pleural scar was the force modifying costal architecture.

#### PROBLEM AND PURPOSE OF THE STUDY

The process of normal osteogenesis is not known, and the sequence of events in osseous regeneration is poorly understood. The literature on these two problems is voluminous and conflicting even in the fundamental concepts. However, Ham's histologic studies of the early phases of the regeneration of bone may be accepted as reflecting the usually adopted beliefs. Ham <sup>15</sup> found that after fracture of the rabbit's rib the adult bone cells died for a distance of 1 to 5 mm. Fragments of bone died also, and this is contrary to the view of Macewen, who said that fragments become centers of osteogenesis. Ham found the lacunas empty or containing pyknotic nuclei. Beyond this area the adult bone cells showed no evidence of proliferation. These observations were borne out by those of Blaisdell and Cowan, Berg and Thalhimer, Mayer and Wehner, Rohde and Mallory. Ham noted that the periosteal osteoblasts after fracture showed mitosis and that gross examination of the periosteum showed it to be thicker and more cellular. The external layers of cells were rapidly dividing, whereas the deeper layers were laying down a cartilaginous matrix. These layers were solid masses of differentiating cells, without blood vessels. Somewhat deeper, new bone formation was found, and here vascularity was noted. Ham pos-

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60. Haight, C.: Complementary Anterior Thoracoplasty for Pulmonary Tuberculosis, *J. Thoracic Surg.* 5:453-470, 1936.

61. Bisgard, J. D.: Ribs Overlying Empyema Cavities, *Arch. Surg.* 27:941-959 (Nov.) 1933.

tulated that the presence of local deposits of calcium salts and a good blood supply are necessary in the metamorphosis of osteogenic cells into bone. He stated, further, that cartilage results from the growth of osteogenic cells in the absence of these factors.

Much of the controversy in the literature hinges on questions of definition and of whether or not the removed periosteum carries with it tiny spicules of bone which may be responsible for subsequent new bone formation. Those who claim that denuded adult bone has osteogenic powers are accused of allowing clumps of cells from the cambium layer of the periosteum to remain on the surface of the graft. That the stripped periosteum does not usually carry spicules of bone with it has been shown by Bisgard,<sup>62</sup> but such questions do not lend themselves well to absolute proof. The thoracic surgeon is only casually concerned in such academic discussions, but he is definitely interested in knowing what he may expect from periosteum and from denuded ribs as seen in the various types of operative procedures. With this idea in mind, an attempt has been made to determine the fate of periosteum, ribs devoid of periosteum and periostealized ribs devoid of blood supply in such procedures as rib resections, thoracoplasties and pneumolyses. Free grafts of bone and periosteum have been studied, and methods of chemical inhibition of rib regeneration have been investigated.

There have been numerous definitions of periosteum, some going so far as to state that periosteum is not an anatomic structure but is rather a region of potential physiologic activity. For purposes of clarity let it be understood that when periosteum is mentioned in this paper that fibrous membrane which is readily stripped from bone by blunt dissection is meant. Its various layers and components will not be considered.

By definition, an osteoblast is a primitive cell which has the ability to develop into osseous tissue. Practically, this definition is not helpful, because it is not histologically possible to differentiate osteoblasts from fibroblasts. For this reason, physicians' knowledge of osteoblasts is largely theoretic, and what they really study microscopically are osteophytes. According to one view, osteoblasts and fibroblasts are identical, but were this true new bone should develop from new connective tissue in the absence of periosteum. On the contrary, as will be shown subsequently, these fibroblasts do not lay down new bone even when they develop in an osseous defect.

#### MATERIAL AND METHODS

In the experimental part of this investigation dogs were used exclusively. The animals were not selected, and their exact ages are unknown. In general, however, it may be said that, judging from the teeth and from the readiness with which

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62. Bisgard, J. D.: Osteogenesis, *Arch. Surg.* 30:748-776 (May) 1935.

the periosteum could be stripped from the ribs, the dogs were young. A few old dogs were used in order to determine the effect of the age factor on the regeneration of bone. All operations were performed with the dogs under pentobarbital sodium anesthesia, 35 mg. per kilogram of body weight being administered intraperitoneally in aqueous solution. The operative site was shaved and prepared with iodine and alcohol. Strict aseptic precautions were used in all operations. In some instances a long oblique muscle-splitting incision was used to expose several ribs, while in others individual incisions were made over each rib which was to be attacked. In the thoracoplasties and similar operations adjacent ribs were used, but in all other experiments alternate ribs were left intact. In many of the dogs three alternate ribs on the right and three on the left were attacked. Linen and silk were used as suture material. When gross infection followed the operation the dog was not included in the series. Roentgenograms of the thorax were taken before the operation, immediately after the operation and at intervals during the period of observation. The dogs were killed at intervals varying from four weeks to four months, and the specimens were then obtained, with several normal ribs on each side for purposes of control. In most instances the specimens were described grossly, roentgenograms were then made and in some cases photographs of the dried specimens were taken. Usually, however, after the roentgenograms were taken the specimens were fixed in solution of formaldehyde, decalcified and sectioned. Decalcification was accomplished with (1) 5 per cent nitric acid, (2) 10 per cent nitric acid and 80 per cent alcohol in equal parts and (3) 5 per cent hydrochloric acid. The latter solution was found to be preferable because the tissues could be cut with greater ease and because the xanthoprotein formed by nitric acid seemed to interfere with staining reactions. All sections were stained with hematoxylin and eosin. Dogs dying within one month were included only if the specimens could be obtained before postmortem autolysis had developed. These early specimens were not used in computing the final results but were included simply to throw some light on the early processes of regeneration of bone.

Several attempts were made to use intravital staining of new bone by the intraperitoneal injection of 10 cc. of a saturated aqueous solution of sodium alizarin sulfonate twice weekly, but in no instance was the attempt successful.

The clinical data are based on patients from the University Hospital, who had empyema thoracis or pulmonary tuberculosis requiring surgical collapse. The specimens were prepared in the same manner as those from the experimental animals.

## EXPERIMENTAL DATA

### ROLE OF PERIOSTEUM IN RIB REGENERATION

*Subperiosteal Rib Resection.*—In 15 dogs, a 3 cm. segment of rib was excised subperiosteally. The remaining periosteal bed was not sutured into tubular form but was left as a flat strip. Specimens were obtained after eight, ten, fourteen, thirty and ninety days. The 2 eight and ten day specimens showed organizing hemorrhage in the periosteal bed, and in 1 there was very early evidence of new osseous formation. The 2 specimens obtained after fourteen days showed early regeneration of bone. In 8 of the 10 specimens obtained after one month complete regeneration had taken place, while in the other 2 there was a small central area not yet filled by new bone. The three month specimen was firmly regenerated, and on section the new bone was seen to have a normal adult type of architecture.

The microscopic sections showed new bone forming from connective tissue. In 20 per cent of the one month specimens cartilage had been formed and was

undergoing ossification, in addition to the new bone which was being formed from connective tissue (fig. 1).

*Rib Resection with Removal of Periosteum.*—In 15 dogs a 3 cm. segment of rib was excised, all of the periosteum being removed with it. This left only the endothoracic fascia to protect the pleura from perforation. Four of the dogs died of perforation and pneumothorax in eight, ten and fourteen days. In 1 dog, when it was killed after one month the lung was adherent to the parietal pleura under the operative site. There was no essential difference in the early and the late specimens in these experiments except in the maturity of the fibrous tissue. In no instance was new bone laid down in an attempt to bridge the defect. The ends of the rib all were smoothly rounded off and were covered by fibrous tissue. In 30 per cent of the specimens there were spurs of new bone where the rib had been excised, the periosteum apparently having been elevated somewhat from the bone by operative trauma (fig. 2).



Fig. 1.—This photomicrograph shows the regeneration of new bone in the periosteal bed one month after the subperiosteal resection of a segment of rib. The transition from cartilage to bone is well shown and the change from connective tissue to bone is also illustrated.

*Interposition of a Flap of Muscle Between the Rib and Its Periosteum.*—In 15 dogs a rib was separated from its periosteum for a distance of 3 cm. A viable flap of muscle was fashioned and interposed between the rib and its periosteum, as described by Alexander.<sup>63</sup> The flap was then sutured so as to maintain this relationship. None of the dogs died of this operation, and there were no adhesions beneath the site when the dogs were killed. Specimens were obtained in eight, ten, fourteen, thirty and ninety days. In the early specimens there were no changes in the denuded rib, and no new bone had been laid down. Of the one month

63. Alexander, J.: Supraperiosteal and Subcostal Pneumolysis with Filling of Pectoral Muscles, *Arch. Surg.* 28:538 (March) 1934.



specimens, 80 per cent showed new bone being formed in the periosteum which had been separated from the rib by a muscle flap. In 60 per cent there was an incomplete bridge of new bone, and in 20 per cent the bridge had formed a complete new rib. Six of the denuded ribs were being absorbed. They were irregularly roughened, and the roentgenogram demonstrated them to be atrophic. Microscopically, when sectioned, some of them were seen to be disintegrating and to be surrounded by a dense layer of fibrous tissue (fig. 3). The three month specimen had a well developed new periosteal rib which showed an adult type of arrangement of the bone cells. The old rib was dead, and fragmentation had set in.

In 3 other dogs a flap of muscle was interposed between the rib and the periosteum in two adjacent ribs. After six weeks each of these specimens showed an incomplete bridge of periosteal new bone, and the denuded ribs were atrophic and smaller in diameter than they had been before (figs. 4 and 5).



Fig. 2.—This photomicrograph shows the dense bed of fibrous tissue formed one month after a segment of rib had been removed with its periosteum. There is no new bone formation.

*Insertion of a Foreign Body Pack Between a Rib and Its Periosteum.*—In 2 dogs the periosteum was separated from five adjacent ribs, and half of a celluloid soap dish was inserted between the ribs and the periosteum, the concavity being turned toward the ribs. These specimens were removed after six weeks. In 1 dog there were pleuropulmonary adhesions beneath the operative site. In both specimens the ribs were irregularly absorbed and were atrophic. The periosteal beds showed varying degrees of regeneration, from spurs of bone at the angles of reflection to complete solid bridges of new bone (fig. 6). This same procedure was repeated in 2 instances, a sterile gauze pack being substituted for the celluloid device and a molded mass of paraffin being used in 1 instance between the ribs and the periosteum. The specimens in which the gauze pack had been used were recovered after six weeks. In both the ribs were being absorbed and were covered by a

layer of granulation tissue. All of the periosteal beds showed new osseous formation from connective tissue (fig. 7). The specimen in which the paraffin pack had been used was obtained after three weeks, and the changes noted were identical with those previously described.

*Multiple Subperiosteal Resection of Ribs.*—In 5 dogs modified thoracoplasties were done. In 4 dogs five ribs were resected, and in the other, in two stages, at weekly intervals, nine ribs were removed. The excised segments extended from the costochondral junction to within 2 cm. of the transverse spinal processes. No external compression was employed. The specimens were recovered one, two and three months after the final stage. In every case paradoxical respiratory motion was noticed for about two weeks after the operation. In two of the experiments old dogs were used, and in 1 after one month and in the other after three months scant new bone formation could be demonstrated. In 1 specimen after one

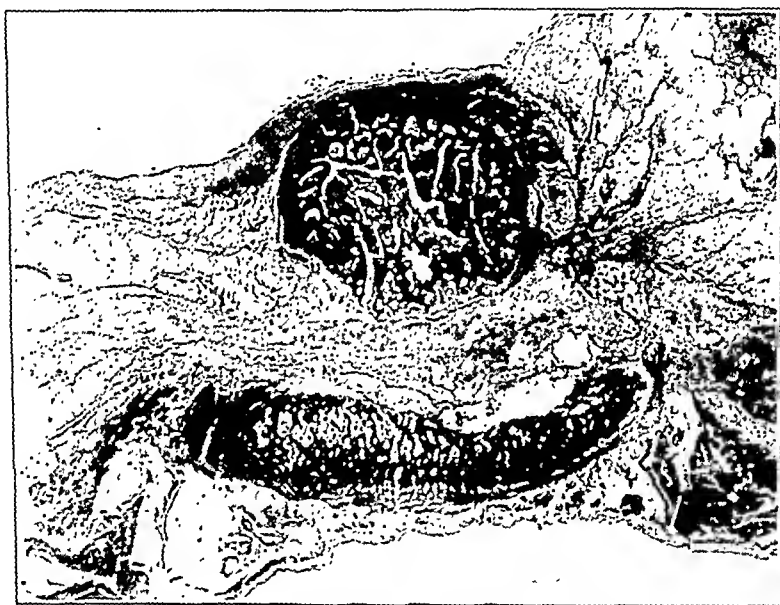


Fig. 3.—This photomicrograph clearly demonstrates the fact that periosteum is capable of new osseous formation. The rib was separated from its periosteum, and a muscle flap was interposed. This shows the result after one month. The old rib shows some irregular erosion of its surface. The new bone in the periosteal bed does not have the contour of adult rib, but in the longer experiments the new rib became more rounded and assumed an adult type of architecture.

month there was firm regeneration in a position of good collapse, while in another there was incomplete regeneration and slight collapse. The two stage, nine rib specimen was removed after two months. It was found that there was very little collapse, owing to the rapid regeneration of the ribs removed at the first stage of the procedure. Some fractures of this new bone were seen. The ribs removed at the second stage were as yet but partially regenerated. In only 1 instance was new bone being formed from ossifying cartilage. In all of the other specimens, the new bone could be seen to be originating from the connective tissue.

*Chemical Osteomyelitis of Ribs.*—In 5 dogs a small drill hole was made in a rib and 1 minim (0.06 cc.) of croton oil was injected into the marrow cavity.

The specimens were recovered after four, eight, fourteen, thirty and forty-two days. After four days there were no gross changes, but microscopically there was a marked increase in the cellularity of the periosteal layer. The eight day specimen was not sectioned, because an extensive subcutaneous abscess developed, and the rib was denuded of its periosteum for 3 cm. on each side of the drill hole. After two weeks there was a moderate amount of new bone around the drill

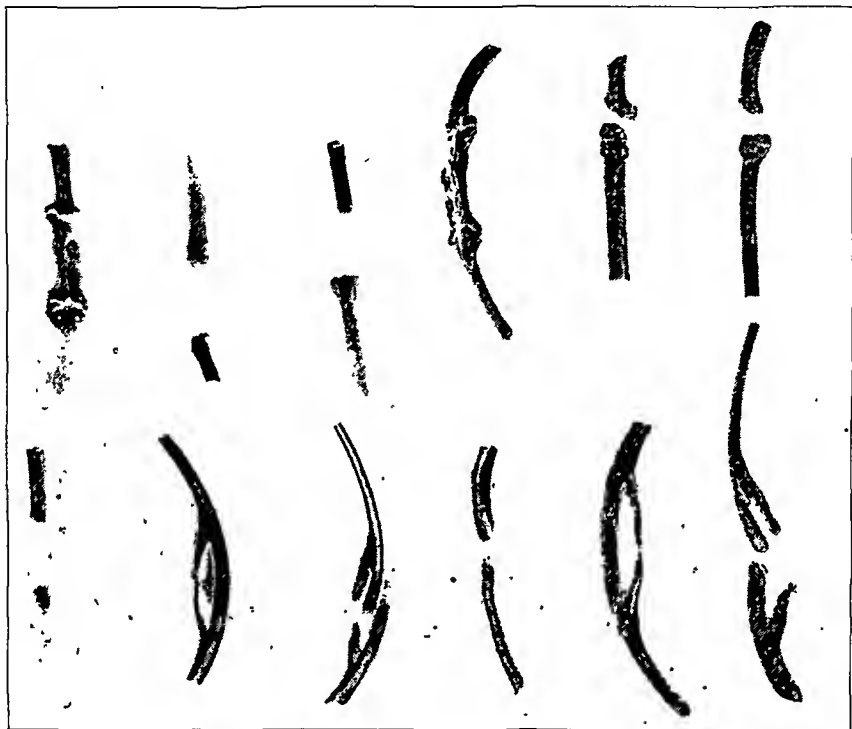


Fig. 4.—The roentgenogram at the left shows the progress of osseous regeneration after one month. In the upper left hand corner, regeneration after subperiosteal resection is seen to be almost complete. Note that regeneration is not originating from the ends of the ribs. In the specimen to the right, the periosteum was removed with the rib segment. Observe the absence of osseous regeneration and the eburnation of the rib ends. The specimen at the top on the right shows the inhibitory effect of the application of Zenker's solution to the periosteal bed. There is a small spur of new bone from the periosteum, with eburnation of the rib end. The periosteal bed of the specimen on the lower left was treated with solution of formaldehyde U. S. P. diluted to 1 to 10. Note the absence of new bone and the more nearly normal appearance of the remaining bone. To the right of it is seen the result of the interposition of a muscle flap between the rib and its periosteum. The bridge of new bone is not quite complete, and there is no atrophy, but some increased density, of the old rib. In the specimen at the bottom on the right is seen the result of fracture when the periosteum is separated from the fragments by a muscle flap. The rib ends are irregularly eroded, and there has been no attempt at healing. The periosteal bridge, again, is incomplete. The figure at the right is a photograph of the same specimens after the drying and removal of the soft tissue. All of these specimens are from the same dog and represent alternate ribs, three on the right and three on the left.

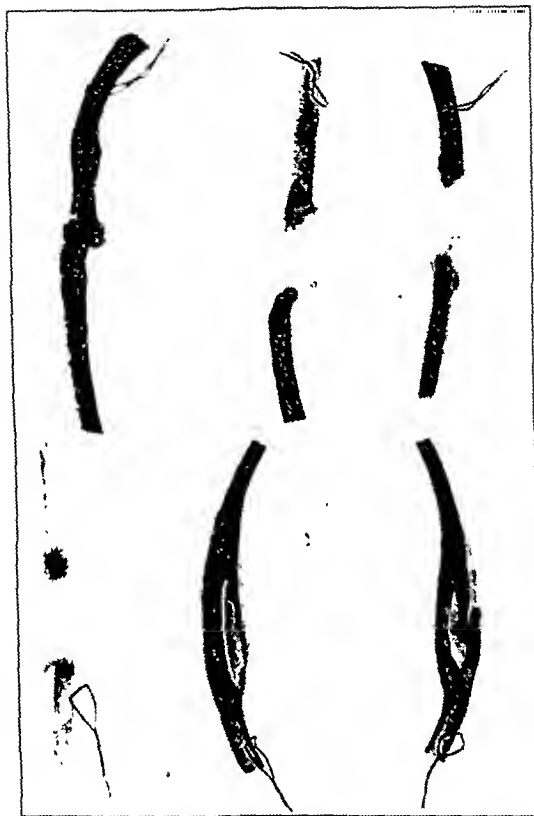


Fig. 5.—This roentgenogram shows the reparative changes after three months. At the upper left, after subperiosteal resection, regeneration is complete and there has been a fracture of the new bone, probably due to respiratory excursion. Note that an adult type of architecture is shown in the new bone. To the right is seen the specimen in which periosteum was removed with the rib segment. There is no regeneration. On the upper right is seen the result of the application of Zenker's solution to the periosteal bed after a subperiosteal rib resection. The lower left hand specimen shows the inhibitory effect of solution of formaldehyde on the periosteal bed. The next specimen shows a periosteal bridge of new bone, formed when the rib was separated from its periosteum by a muscle flap. In the specimen at the lower right there has been no attempt at repair of the fracture when the periosteum was separated from the fragments by a muscle flap. The rib fragments are churned and irregularly absorbed.



Fig. 6.—This photograph shows the result of an experiment in which, six weeks previously, the periosteum was separated from a 6 cm. area on five adjacent ribs and a celluloid device was inserted between the ribs and their periosteum. This rib clearly shows the firm and extensive formation of new bone from the periosteum. The original rib is seen to be atrophic and partially absorbed.

hole. This new bone almost completely surrounded the rib and apparently arose from the periosteum, blending into the surrounding fibrous tissue. After one month there was a large amount of new bone, apparently arising in a similar manner. The six week specimen showed a moderate amount of new bone, which now had taken on an adult type of architecture.

#### ROLE OF PERIOSTEUM IN THE HEALING OF COSTAL FRACTURES

*Separation of the Periosteum from the Site of the Fracture by a Flap of Muscle.*—In 15 dogs a rib was exposed and the periosteum was incised for a



Fig. 7.—This roentgenogram shows the result six weeks after the insertion of a sterile gauze pack between the periosteum and the ribs. Periosteal new bone is well shown, and there is marked atrophy of the deperiostealized ribs.

distance of 3 cm. The periosteum was then bluntly separated from the rib and a flap of viable muscle was interposed between the rib and its periosteum. Care was taken to jeopardize the blood supply as little as possible, and the trauma was minimal. After the flap of muscle had been sutured in place, a simple clean fracture of the denuded rib was accomplished over the center of the flap by means of the rib shears. The effect of this procedure, then, was to produce a fracture of the rib, the fragments being devoid of periosteum for 1.5 cm. on each side of the fracture. One specimen was obtained after eight days, 1 after ten days, 2 after fourteen days, 10 after thirty days and 1 after ninety days. In the specimens

obtained within one month there were no gross evidences of new bone formation. The periosteum in 2 specimens, however, showed new bone in an early stage when sectioned. In 1 instance a fragment of rib punctured the pleura, and the dog died of pneumothorax. In 1 instance the lung was adherent to the pleura under the operative site. From one of the fragments a mass of endosteal granulation tissue was protruding.

In one month specimens there was no evidence of new bone formation from the fragments devoid of periosteum. In every instance the fragments were more or less firmly bound together by dense fibrous tissue. In most of the specimens the ends of the fragments were of smaller diameter than the remainder of the rib, and on roentgenoscopic examination they were seen to be eburnated. Microscopic section showed the lacunas to be empty, and there was evidence of absorption. In the periosteum, separated from the fragments by the muscle graft, 7 of the 10 specimens showed new bone formation. In some instances the new bone was represented by spurs at the angles of reflection of the periosteum from the bone, while in others there was an incomplete bridge of new bone. In the specimen removed after three months there was a heavy and complete periosteal bridge of new bone. There was dense fibrous union of the fragments, which were becoming absorbed.

#### IMPORTANCE OF THE PERIOSTEAL BLOOD VESSELS IN REGENERATION OF BONE

*Destruction of the Blood Supply from the Intercostal Bundles.*—In 19 dogs the intercostal bundles were carefully dissected from two to six adjacent ribs, the periosteum being left intact on the ribs. In this manner all blood supply to the periosteum from the intercostal bundles was destroyed. In 5 dogs these intercostal bundles were allowed to fall back into their normal positions, while in the other 14 the bundles were separated from the ribs by a celluloid device or by a gauze pack. Specimens were studied after six weeks. In the dogs which died early the periosteum was found to be necrotic and to have sloughed from the ribs in irregular patches. In the 5 dogs in which the intercostal bundles had been allowed to fall back into position the periosteum had been able partially to revascularize itself, but in each instance there was found definite atrophy of bone on roentgen examination. In those in which foreign bodies had been interposed between the ribs and the intercostal bundles the degree of rib absorption varied markedly. In some dogs, the roentgen study showed simply surface roughening and rarefaction. In others there was definite absorption, with spurs of new bone at the edges. Occasional nodules of new bone had formed from the haversian canals. In 2 instances all of the ribs in the operative area had undergone complete solution of their continuity and there was a draining sinus through the wound from which bony spicules were being extruded (fig. 8). In all of the specimens the ribs which were being absorbed were covered by heavy layers of granulation tissue. In 1 specimen the filaments of granulation tissue measured 8 to 10 cm. in length. The gauze pack had eroded the pleura, and these filaments were protruding into the pleural cavity. The remainder of the pleura under the area of the pack was thickened.

#### SPECIFICITY OF FREE PERIOSTEAL GRAFTS

*Abdominal Subfascial Implants of Rib Periosteum.*—In 7 dogs a 2 cm. segment of rib was excised with its periosteum. The periosteum was then bluntly stripped from this fragment and, free from bone spicules, so far as gross examination

could determine, was implanted into the abdominal wall just beneath the anterior sheath of the rectus abdominis muscle. Hemostasis was adequate. One dog died from some other cause on the ninth day. Specimens were recovered from the other animals after six weeks. The nine day specimen showed no evidences of new bone formation on gross examination, in the roentgenogram or on section. There was a dense inflammatory reaction at the site of implantation. The 6 specimens recovered after six weeks showed a nodule of new bone in every instance. The nodules ranged from 2 mm. to 2 cm. in diameter and did not tend to assume an adult type of architecture. In no instance was formation of cartilage noted (fig. 9).

#### FATE OF BONE DEVOID OF PERIOSTEAL COVERING

*Deperiostealized Ribs.*—These data are drawn from experiments cited in other connections in this paper, and the procedures need not be described in detail again.



Fig. 8.—This roentgenogram shows the result of an experiment in which, six weeks previously, the intercostal bundles were carefully dissected away from these ribs, leaving the periosteal covering intact. A sterile gauze pack was then inserted between these periostealized ribs and the muscle bundles. A draining sinus formed in the wound, from which bony spicules were extruded. Solution of continuity of ribs is shown by adjacent periosteal new bone, probably stimulated by the local irritation of the pack.

Briefly, in 38 dogs ribs were divested of their periosteal covering and separation was maintained by muscle grafts or by foreign body packs. The ribs were studied microscopically and by roentgenogram at intervals varying from eight days to six weeks. In each instance there was death of the bone with slowly progressive atrophy and absorption by adjacent granulation tissue, which grew in and attempted to revascularize the dead bone. In no case was there definite evidence of new bone developing from the old, although new connective tissue was abundant.

## FATE OF OSSEOUS AND OSTEOPERIOSTEAL TRANSPLANTS

*Subfascial Implantation of Periosteum-Free Segments of Rib.*—In 7 dogs a 2 cm. segment of rib was excised and stripped of its periosteum. This fragment of denuded bone was then implanted into the abdominal wall just beneath the anterior sheath of the rectus abdominis muscle. Hemostasis was secured. One dog died on the ninth day from some other cause, and specimens from the other animals were recovered after six weeks. The nine day implant was apparently dead, the lacunas being empty and fragmentation of the specimen being already present. The 6 specimens recovered after six weeks showed fragmentation and evidences of absorption. Some of these implants were almost entirely absorbed, being represented by tiny spicules embedded in a heavy layer of granulation tissue. Practically all of the lacunas were empty, and the interstices were being invaded by new

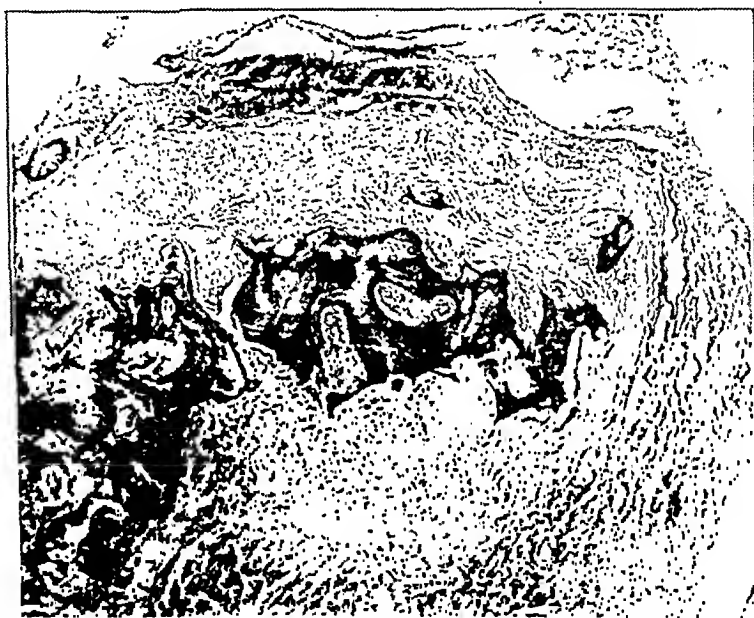


Fig. 9.—This photomicrograph of a fragment of free periosteum, taken six weeks after its subfascial implantation, shows the development of new bone from connective tissue elements.

connective tissue (fig. 10). In 2 instances there was evidence of new osseous formation, but it cannot be definitely stated that this new bone originated from the old. It may be argued that the presence of abundant vascularity and calcium salts leads to metaplasia of the connective tissue.

*Subfascial Implantation of Periosteum-Covered Segments of Rib.*—In 2 dogs similar implants were made, except that the periosteum was allowed to remain on the graft. After six weeks the specimens were removed. One specimen apparently was living, showed no evidence of absorption and had formed a small amount of new bone under the periosteum. The other specimen had been absorbed almost completely and there was no evidence of the formation of new bone.



## EFFECT OF AN UNDERLYING CAVITY ON FORMATION OF BONE

*Separation of Periosteum-Covered Ribs from the Intercostal Bundles by Foreign Body Packs.*—In an effort to determine whether or not bone will proliferate, as does pleura, in an attempt to obliterate an adjacent cavity, the following experiments were carried out: In 6 dogs the intercostal bundles were carefully dissected from six adjacent ribs, the periosteal covering being left intact. A portion of a celluloid soap dish was then inserted between the endothoracic fascia and the periostealized ribs. Three of the dogs died of erosion of the pleura, pleural effusion and pulmonary collapse. After six weeks the remaining dogs were killed. In 1 dog thickening of the parietal pleura beneath the foreign body had developed. In every instance the ribs were found to be covered by granulation tissue, and nodules of new bone had developed over the surface, apparently growing from



Fig. 10.—This photomicrograph of a deperiostealized graft of bone, taken six weeks after its subfascial implantation, shows it to be dead. The lacunae are empty, and fragmentation is beginning.

the haversian canals (fig. 11). Rather large spurs had formed at the edges of the artificial cavity, but there was no demonstrable evidence of formation of new bone on the inner aspect of the ribs in order to close the cavity. When sectioned, the ribs were seen to be dead, and the follicles were empty. The dead bone was being vascularized and absorbed by adjacent new granulation tissue. In one instance the artificial cavity contained a caseous white material. In the others it contained serous fluid. Aspiration had been necessary in order to remove this fluid on several occasions during the course of the experiment. This experiment did not fulfil its purpose, because the periosteal blood supply from the intercostal bundles was cut off, and apparently the endosteal blood supply is insufficient to maintain viability in the dog's rib.

## INHIBITION OF RIB REGENERATION BY CHEMICAL AGENTS

*Subperiosteal Rib Resection with Zenker's Solution Applied to the Periosteal Bed.*—In 15 dogs a 3 cm. segment of rib was resected subperiosteally. The periosteal bed and the ends of the rib were then treated with freshly prepared Zenker's solution. Care was taken not to use an excess of fluid, and the adjacent tissues were protected as well as possible. Two dogs died of pneumothorax, and Zenker's fluid was found to have caused necrosis and perforation of the pleura. In 1 instance pleuropulmonary adhesions had formed beneath the operative site. Specimens were taken after eight, ten, fourteen, thirty and ninety days. The early specimens were characterized at gross examination and when sectioned by a shaggy, necrotic area representing the periosteal bed. In the later specimens this necrotic tissue had been absorbed, and the sections showed a mass of fresh granulation tissue infiltrated by leukocytes, especially neutrophils. In no specimen was there any evidence of formation of new bone from the periosteal beds. In 3



Fig. 11.—The roentgenogram at the left shows the position of the celluloid device forming a subperiosteal extrapleural cavity. This device was placed between the ribs and the pleura, the periosteum being left on the ribs but the intercostal bundles being dissected off. The roentgenogram at the right shows the specimen removed after six weeks, demonstrating slight atrophic changes in the periostealized ribs over the cavity, deprived of their intercostal vascular supply. There is some periosteal new bone.

specimens there was a small spur of new bone at the point of section of the rib. This bone seemed to be developing from connective tissue.

*Subperiosteal Rib Resection with Solution of Formaldehyde Applied to the Periosteal Bed.*—In 15 dogs a 3 cm. segment of rib was resected subperiosteally, and the periosteal bed was treated with solution of formaldehyde U. S. P. diluted 1 to 10. In 1 dog pleural necrosis occurred, with perforation and death. One dog showed pleuropulmonary adhesions beneath the operative site. The specimens were recovered after eight, ten, fourteen, thirty and ninety days. There was much less necrotic tissue than after the use of Zenker's solution. After the use

of solution of formaldehyde the periosteal bed most often contained a mucoid material of gelatinous consistency. In no instance was there periosteal new bone, and in only 1 instance was there a spur from the end of the rib (fig. 12).

*Use of Solution of Formaldehyde in Periosteal Bed After Thoracoplasty.*—In 5 dogs a modified thoracoplasty was done, four, five or six ribs being excised subperiosteally. The ends of the ribs and the periosteal beds were then treated with solution of formaldehyde U. S. P. diluted 1 to 10. In 3 of the dogs multiple stage procedures were attempted, but the animals died after the second stage. In 1 instance death was due to pleural perforation by the sharp end of a rib. One specimen was obtained after two months. There was no osseous regeneration and but little spur formation. The other specimen was obtained after four months. Healing had taken place by the formation of dense fibrous tissue. There was no evidence of new bone formation. In these animals, as compared with those on

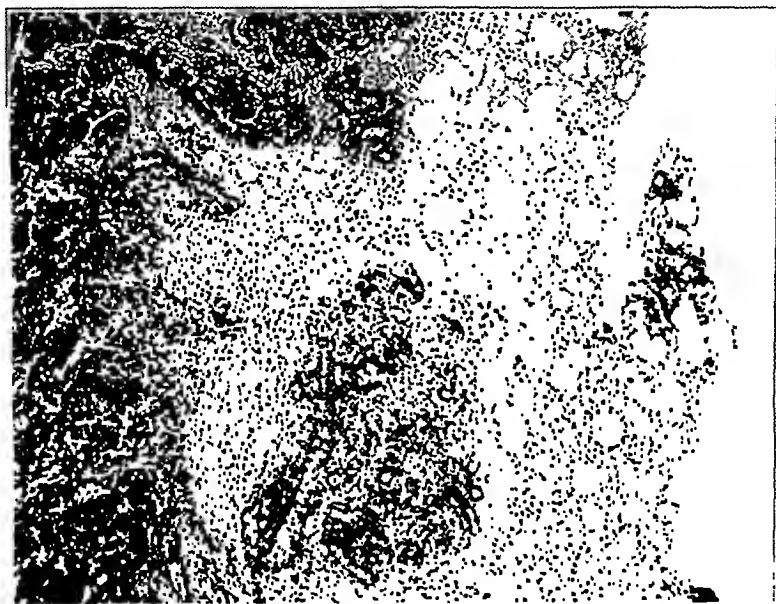


Fig. 12.—This photomicrograph shows granulation tissue and new fibrous tissue, demonstrated by section one month after the periosteal bed was treated with solution of formaldehyde. This reaction is less severe than that seen following the use of Zenker's solution. There is no new osseous formation.

which thoracoplasty was performed without treatment, wound healing was slightly delayed, but this delay was not more than three or four days. In the dogs treated with solution of formaldehyde dyspnea and paradoxical respiratory motion were observed to disappear much earlier than in the untreated dogs. Apparently this resulted because of the stimulation of proliferation in the connective tissue after the application of solution of formaldehyde, causing rigidity of the wall to follow during the first week. This did not interfere with collapse, however, as collapse was found to be much more nearly complete in the dogs treated with solution of formaldehyde. The latter observations cannot be supported by photographic or kymographic proof.

## CLINICAL MATERIAL

## RIBS OVERLYING EMPYEMA CAVITIES

*Chronic Empyema.*—In 6 cases of chronic empyema, ranging from three months to several years in duration, ribs were secured for study after unroofing procedures. Roentgenograms in each case showed new bone formation along the inner inferior borders of the ribs. The normal costal contour was lost, and the general shape was changed from the normal ovoid to square or triangular. There was a direct correlation between the duration of the empyema and the amount of new bone laid down. In the cases of empyema of longer duration, normal costal architecture was entirely lost, there being no division into cortex and medulla. There was also a direct correlation between the size of the rib and the

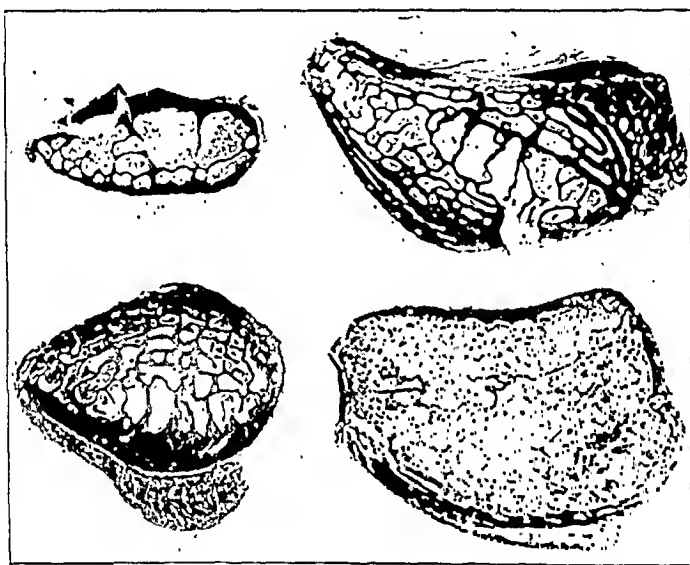


Fig. 13.—These photomicrographs of rib sections from the clinical material show the new osseous formation in cases of empyema thoracis. In the upper left is a section from a normal rib removed at thoracoplasty and studied as a control. Below it is seen the new bone formed in a case of empyema of two months' duration. The rib on the upper right demonstrates the amount of new bone in a case of empyema of four months' duration and below it is a section of rib obtained in a case of empyema of two years' duration. All sections are shown at the same degree of magnification.

duration of the empyema. The new bone apparently was formed subperiosteally and was deposited in successive layers over the empyema cavity (fig. 13).

*Acute Empyema.*—The ribs in 10 cases of acute empyema were studied by roentgenograms and sections were taken through the resected segments. In all cases the disease was of less than four weeks' duration, and in no case was any new bone demonstrable.

REGENERATION OF RIBS AFTER THORACOPLASTY  
AND RIB RESECTION

A study of roentgenograms taken after thoracoplasty shows that rib regeneration usually can be demonstrated in three or four weeks after the operation. The regeneration tends to take the form of flat sheets of bone with many synostoses, owing to the fact that the new bone is formed from the flat expanses of periosteum, which do not have their original tubular form. In some instances new bone can be demonstrated as early as two weeks after thoracoplasty, and in certain cases this new bone formation definitely interferes with surgical collapse therapy. In several cases it has been necessary secondarily to excise this regenerated bone in order to achieve adequate collapse from subsequent procedures. Probably, however, more frequent causes of revision of thoracoplasty are (1) inadequate external compression and (2) inadequate original thoracoplasty.

## INHIBITION OF REGENERATION

In a series of cases of acute and chronic empyema, abscess of the lung and surgical tuberculosis the periosteal beds have been treated with solution of formaldehyde U.S.P. diluted 1 to 10, and the effect on regeneration of bone has been observed for three months. In this series of about 12 cases, there has been no evidence of new bone formation in 10, even after three months, and this is an interval much longer than is usually allowed to elapse between stages of thoracoplasty. In 2 cases there was some regeneration after four weeks.

With empyema and abscess of the lung, in which healing is normally slow, the disadvantage of having new bone formed before the underlying cavity has closed is obvious. I have seen several cases in which the regenerating rib so tightly encircled the drainage tube as to necessitate a secondary resection.

In the cases of thoracoplasty no delay in the healing of the wound could be noticed, and thus far no contraindication to the use of solution of formaldehyde on the periosteal beds has been demonstrated.

## COMMENT

There are many factors which must be taken into consideration in explaining the various conflicting reports found in the literature, and it is probable that when judged by the same criteria these results could be brought into accord. For example, in experimental work the age of the animal is very important, as is the degree of operative trauma to the local vascular supply. Also, in speaking of free bone grafts, it is necessary to consider the size, because whereas small grafts may

readily acquire a new blood supply and grow, larger grafts may become necrotic before such a supply can be established. The vascularity of the site into which the graft is implanted must also be considered. One must remember that much of the original work was done before the days of aseptic surgery and that consequently infection must have modified the results considerably. Too, there has been some discussion as to whether the cambium cells should be classed with the periosteum or with the bone. This would, of course, influence the interpretation of results. Consideration of these and other factors may clear up many apparent discrepancies in reported results. Most reports have been written in support of one of the theories of regeneration of bone without consideration of the fact that each of these theories may obtain under different conditions and in different locations.

The periosteum of the dog's rib is definitely osteogenic, and that the periosteum does not serve merely as a limiting membrane is shown by the fact that in these experiments the periosteum was invariably left as a flat sheet and was not tubulized. It has been observed that in the presence of a good blood supply periosteum tends to form new bone, whereas in the absence of vascularity cartilage or fibrous tissue is formed. This observation probably has some bearing on the question of nonunion of fractures.

The periosteum in every experiment has been found to be a definite anatomic structure. In young animals it is easily stripped from the rib and is capable of producing new bone, but in old animals it is a thin layer, densely adherent to the rib and relatively incapable of forming new bone. Wherever new bone has been formed the periosteum can be seen to be the site of extreme cellular activity. Periosteum is not necessarily a layer made up of specifically osteoblastic cells, however, for regenerated ribs become covered with a layer of fibrous connective tissue which cannot be differentiated from the original periosteum.

In 91 per cent of these experiments new bone could be seen to be developing from connective tissue elements, apparently derived largely from periosteal activity but probably also partially from the adjacent tissues, as fibroblasts cannot be differentiated from osteoblasts. In a relatively small number of instances cartilage had been formed and could be seen to be undergoing ossification in some places. In no instance was the new rib preformed in cartilage.

It does not seem reasonable to suppose, and these experiments do not give evidence, that adult fibrous tissue can become bone by metaplasia or that adult bone cells can escape from their lacunas and become foci for the formation of new bone. It seems quite rational, however, to expect the ubiquitous fibroblast to assume osteogenic prop-

erties under proper conditions of vascularity and availability of calcium. This explains the phenomenon of heterotopic bone formation and may explain the growth of free bone grafts, although the exact role of endosteum and the haversian system cannot properly be evaluated.

The removal of periosteum together with a rib segment effectually inhibited osseous regeneration, and there was no attempt to bridge the defect. The ends of the ribs became rounded, and the marrow cavities were sealed off by fibrous tissue. This probably illustrates the development of nonunion and pseudoarthrosis following a fracture in which the fragments are separated by periosteum over their ends or by interposed soft tissue.

Interposition of a muscle flap or of a foreign body pack between a rib and its periosteum resulted in absorption of the denuded rib and formation of a new rib in the periosteal bed. This indicates not only that the periosteum is capable of laying down new bone but that its normal function is to supply the bone with adequate nourishment. This is borne out by the fact that similar osseous necrosis resulted from destroying the intercostal blood supply to the periosteum. The denuded bone first became atrophic and then became covered by a layer of granulation tissue,<sup>64</sup> which began the work of fragmenting and absorbing the dead bone.

Osseous, periosteal and osteoperiosteal implants into muscle grew with varying degrees of success, seemingly in direct ratio to the ease and speed with which a new blood supply was established. Periosteal grafts grew more frequently than did osseous grafts, as might be expected because of the fact that a thin sheet of periosteum is more easily vascularized than is a segment of dense bone. With regard to free bone grafts, one cannot be sure that the new bone has not developed from elements of the endosteum or from the haversian system.

Costal fractures showed no tendency to heal if the fragments were separated from their periosteum by an interposed flap of muscle. The fragments became eburnated and partially absorbed. There was no evidence of callus from the endosteum, but there was a reaction in the fibrous tissue with consequent immobilization. New bone developed in the periosteal bed beneath the flap. These experiments indicate that the endosteum in the rib of the dog has feeble, if any, osteogenic properties and that the healing of the costal fractures is chiefly dependent on the presence of periosteum on the fragments.

In the experimental series it was seen that early rib regeneration hindered the progress of collapse with the multiple stage type of

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64. Phemister, D. B.: *Necrotic Bone and the Subsequent Changes Which It Undergoes*, J. A. M. A. **64**:211-216 (Jan. 16) 1915.

thoracoplasty. The stages were spaced at biweekly intervals, and new bone had already begun to develop before the next stage was attempted. Complete regeneration of the ribs was the rule in four weeks. These new ribs sometimes showed the presence of spontaneous fractures, probably due to respiratory excursion and usually lacked the normal outward bowing.

Zenker's solution and solution of formaldehyde U.S.P. diluted 1 to 10 when applied to the periosteal beds after resection of ribs were found to inhibit regeneration for at least four months. Zenker's solution exerted a more severe reaction, causing necrosis of tissue, pleural perforations, delayed healing of the wound and, in some instances, pleuropulmonary adhesions. Solution of formaldehyde caused a much less severe reaction, with a consequently lower percentage of morbidity and mortality.

In the experimental thoracoplasties in which solution of formaldehyde was used on the periosteal beds, paradoxical respiratory motion was present for a shorter period than when the treatment was not given, probably because of the greater stimulus to the formation of fibrous tissue given by the formaldehyde. The chest walls of the subjects were actually rigid sooner than those of the untreated subjects. Collapse was more nearly complete in the subjects in which solution of formaldehyde was used, probably because of the absence of regenerated bone. The healing of the wound was delayed only slightly.

Clinically, ribs overlying chronic empyema cavities were found to show new osseous formation on their inner and lower aspects. The entire costal contour and architecture were altered, and the changes seemed to be in direct ratio to the duration of the process. Such new bone formation could not be demonstrated in cases of empyema of less than four weeks' duration, and these changes could not be used to measure the size of the underlying cavity on roentgenoscopic examination.

Early rib regeneration after thoracoplasty was found to interfere with adequate pulmonary collapse in some cases of pulmonary tuberculosis treated by multiple stage thoracoplasty. I believe that this can be obviated by the use of solution of formaldehyde U.S.P. diluted 1 to 10 on the periosteal beds during the first stage of the procedure. This allows for a longer interval between stages, if necessary because of occurrence of traumatic infection or the spread of tuberculosis to the opposite lung. Solution of formaldehyde need not be used in the subsequent stages. No fear of a permanently pliable chest wall need be entertained, because the operative area of the first stage of the procedure is adequately protected by the scapula and by the heavy muscles of the back and shoulder.



## CONCLUSIONS

1. Periosteum is definitely osteogenic and is a very important source of blood supply to bone.

2. Periosteum is the most important source of regeneration of bone and its presence is necessary for union in case of fracture.

3. The growth of osseous and periosteal transplants is in direct ratio to their ability to establish an adequate blood supply.

4. Solution of formaldehyde is superior to Zenker's solution as an inhibitor of costal regeneration, the inhibition which it produces lasting for at least four months.

The application of solution of formaldehyde U.S.P. diluted 1 to 10 to the periosteal beds in a series of clinical cases has not been accompanied by delayed healing of the wound or by any other disadvantage. No positive results can be stated as yet, because the series is small and the follow-up interval is too short.

The application of solution of formaldehyde to the periosteal beds is advocated in all resections of the ribs for the drainage of empyema or abscess of the lung. It is also advocated in first stage thoracoplasties, with the reservation that it should not be used in the bed of the first rib because of possible damage to the adjacent nerves and vessels by the formation of scar tissue.

5. The chemical inhibition of rib regeneration should not be employed in the Semb type of apicolysis. because in this operation the new bone aids in maintaining collapse of the lung.

## APPENDICITIS AT THE JAMESON MEMORIAL HOSPITAL

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NEW CASTLE, PA.

Fifty-one years ago Reginald Fitz, of Boston, read his classic paper on "Perforating Inflammation of the Vermiform Appendix with Special Reference to Its Early Diagnosis and Treatment." It has been estimated that since that time ten thousand papers have been written on the subject.<sup>1</sup> In one sense, certainly, there is little left to be said. Yet, considering the magnitude of the problem and the fact that every hospital plays a part in the fight against appendicitis, I can probably find excuse for describing how the hospital at New Castle, Pa., is coping with the problem.

Appendicitis assumes the proportions of a problem in public health when one realizes that, while it is a disease which if promptly recognized and properly treated should be practically free from mortality, it produces an annual death rate in the United States which equals the combined annual death rates from ectopic pregnancy, pyosalpinx, gallstones and all diseases requiring intervention in the pancreas, spleen and thyroid, nearly equals that from gastric ulcer, duodenal ulcer, intestinal obstruction and gallstones, exceeds that from measles, scarlet fever and whooping cough together, equals that from automobile accidents and nearly equals that from diabetes.<sup>2</sup>

A further reason that has compelled the medical profession to take stock of appendicitis frequently is that many writers until recently were much annoyed by the tendency for the death rate from this disease to increase. The death rate in the United States in 1928 for appendicitis was 15.3 per hundred thousand, while by 1933 it was 18 per hundred thousand. On the other hand, in the "Statistical Bulletin" for August 1936, there is a study on the recent decline in the death rate from appendicitis.<sup>3</sup> This study is based not on the population as a whole but on Metropolitan industrial policyholders. The standardized death rate from appendicitis in this group dropped steadily

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From the Jameson Memorial Hospital.

1. Elkin, D. C., and Glenn, W.: Acute Appendicitis, *J. M. A. Georgia* **25**: 113 (April) 1936.

2. Wright, T.: Appendicitis: General Survey and Statistics, *New York State J. Med.* **33**:673 (June 1) 1933.

3. Recent Decline in Appendicitis Death Rate, *Statist. Bull., Metropolitan Life Insur. Co.* **17**:4 (Aug.) 1936.

from 14.3 per hundred thousand in 1931 to 11.5 in 1935, a decrease of 20 per cent. According to this same source, comparable data for the general population are available and show the same general downward trend.

It is not unlikely that this healthy trend is due to critical analysis of the situation by hospitals, medical societies and interested physicians. It is stated that because of self study and resulting educational propaganda Philadelphia has attained a death rate from appendicitis that is 81 per cent lower than the average of one hundred and seventeen other cities. When allowance is made for errors, this is shown to mean that Philadelphia has made a flat reduction of 75 per cent in its mortality from appendicitis.<sup>4</sup>

The New York Academy of Medicine has instituted a serious study of this problem and its Committee on Public Health Relations has been authorized to make a further study along the lines of the recent investigation of maternal welfare.

It is suggested that every surgeon and the staff of every hospital should prepare to answer the following questions:<sup>5</sup>

1. What mortality do you encounter from appendicitis?
2. In what percentage of cases is operation performed before rupture occurs?
3. In the cases in which rupture takes place, who is the cause of the delay: (a) the patient; (b) the family physician; (c) the surgeon?
4. Are cathartics responsible for the rupture?
5. If so, by whom were they administered: (a) the patient; (b) the patient's family; (c) the druggist; (d) the physician?
6. In the cases in which complications occur, has operation been immediate or deferred, and what mortality have you encountered in this special group of cases?

It is with the purpose of self analysis and of answering such questions as these in order to know where they stand on this problem that the staff of the Jameson Memorial Hospital, at New Castle, Pa., has undertaken a study of appendicitis. To gather material for this study it was decided to survey the records of all patients discharged from the hospital in 1935 and 1936 with a final diagnosis of appendicitis.

The total number of admissions to the hospital for this two year period was 5,943. The number of patients for whom a final diagnosis of appendicitis was recorded was 440 for the two years. Not allowing for readmissions or for the fact that some of the patients were not

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4. Foltz, J. A.: The Rising Mortality in Appendicitis and What We Are to Do About It, *J. Arkansas M. Soc.* 33:49 (Aug.) 1936.

5. Ramsdell, E. G.: Appendicitis: A Challenge. *New York State J. Med.* 35:673 (July 1) 1935.

operated on and thus the diagnosis was not proved to be correct, for 1 of every 14 patients who left the hospital appendicitis was at least one of the conditions diagnosed.

Of these 440 patients, 23 (5.2 per cent) were not operated on. These 23 patients were managed by twelve different doctors, 15 (65.2 per cent) of them by surgeons and 8 (34.8 per cent) by internists and general practitioners.

In the group of patients on whom operation was not performed there was a mortality of 8.7 per cent (2 patients). One patient, a 32 year old woman, was moribund on admission. She had been ill for two weeks, and, as far as could be learned, a physician had not been consulted until the fatal generalized peritonitis had set in. She died after five hours, during which time the Ochsner treatment for peritonitis was instituted.

In the other case with a fatal outcome, that of a 79 year old woman, the history, results of physical examination and observations in the laboratory were characteristic of appendicitis. Operation was deferred because the patient presented also auricular fibrillation and edema of the ankles. However, after eight days in the hospital, she died from a cerebrovascular accident. As no autopsy was held, there is no certainty about the abdominal condition, which may well have been an embolic phenomenon.

Another 9.7 per cent (2 patients) of those on whom operation was not performed returned at a later date. One, a 10 year old girl, returned to the hospital ten months after her first admission, having suffered an abdominal attack of two days' duration. The microscopic examination of her appendix was said to show no pathologic condition. The other patient, a 47 year old man, who had been having abdominal upsets for years, returned to the hospital after two months. An appendectomy was done, and microscopically the appendix showed the reaction of chronic inflammation and fibrosis.

One of the 23 patients not submitted to operation had hemophilia. He was a 26 year old white American who four days before admission had diffuse pain in the abdomen, later localized in the right lower quadrant. He experienced nausea and vomiting. He had taken a cathartic by mouth. On admission, his temperature was 101 F. and his pulse rate 100. Moderate tenderness and muscular spasm were found in the right lower quadrant of the abdomen, and a mass was outlined in this area. No rectal examination was recorded. The urine was normal, and the leukocyte count was 15,400 with 86 per cent polymorphonuclear neutrophils. Because of the hemophilia it was deemed wise to treat the patient expectantly, especially since the presence of a mass in the right lower quadrant indicated a tendency toward localization. To relieve his discomfort acetylsalicylic acid and codeine were given. Fluids were administered parenterally and ice bags were applied to the abdomen.

The mass in the right side tended to subside. The temperature ranged between 101 and 104 F. and stayed at normal after the fifteenth day. Daily differential blood counts were made. On the nineteenth day the patient was discharged in good condition.

In the main the patients on whom no operation was performed were treated as follows: Nothing was given by mouth; ice bags were placed on the abdomen, and in some cases enemas were given. Frequent differential blood counts were made.

It is important to ask why operation was omitted in these cases, because it is the consensus of the hospital staff that operation is advisable when appendicitis presents itself. As has been seen, 1 patient was not operated on because age and cardiac decompensation rendered the prognosis unfavorable; a second because his condition was complicated by hemophilia, and a third, because she had diffuse peritonitis and was moribund (she died five hours after admission). Seven more patients were not subjected to surgical intervention because obviously they did not have appendicitis, although it was mentioned in the final diagnosis. Two probably had renal colic; 2 others had pain associated with the onset of menstruation; another 2, it seems probable from the records, had salpingitis. One patient apparently had gastroenteritis from infection caused by food. In 3 cases, in which the symptoms were mild and rapidly subsiding, diagnoses of subacute appendicitis were made and the patients were sent home after one day in the hospital. In 5 cases, with histories of repeated attacks of pain on the right side, diagnoses of chronic appendicitis were made. In 1 of these the patient returned to the hospital two months later and was submitted to operation.

Perhaps operation was not performed in the other cases of chronic appendicitis because the surgeons were acquainted with Bettman's study, made in 1928, which showed that of a series of 5,664 cases in which operation was performed for chronic appendicitis 40 per cent of the patients were unrelieved, 11.6 per cent were made worse and 1.7 per cent died. On the other hand, Charles Mayo pointed out that the day in which appendicitis was classified as of one of two types, the acute and the remunerative, is past. Dr. Mayo believes that there is a variable syndrome which is caused by chronic appendicitis. The problem is to recognize it preoperatively. Barber and Charles Mayo reviewed 100 cases in which they had performed exploration for certain unexplained abdominal symptoms after careful study. In these cases only the appendix was removed, and in each case it was reported to be chronically diseased. Five years later a check was made on the 100 patients. Sixty-nine said that they were cured, 21 that they were materially benefited and 9 that they were not helped. Although 2 of the 9 were better, they felt that the improvement was due to the removal of infected teeth and tonsils.<sup>6</sup>

6. Mayo, C.: Appendicitis, *Southwestern Med.* 18:397 (Dec.) 1934.

There were 5 more patients not submitted to operation in the present series whose condition was diagnosed as acute appendicitis. One was a 73 year old woman who had the typical history, tenderness without spasm and leukocytosis. No doubt temporizing measures were employed in her case because of her age and the opinion that her condition was controllable by conservative therapy. Another of these 5 patients returned ten months later in the midst of a second attack. In the cases of the other 3 the history, signs and laboratory findings pointed to acute appendicitis and that was the diagnosis. The reasons for not having operated are not apparent from a study of the records.

A review of the 417 cases in which operation was performed indicates that 20, or 4.8 per cent, of them were those of girls and women from 16 to 42 years of age, submitted to operation for gynecologic diseases, whose appendixes were incidentally removed. Pathologic report on these appendixes indicated that 30 per cent were normal, 60 per cent chronically diseased and 10 per cent subacutely inflamed. There were no deaths in this group.

Another patient, an 18 year old boy, was awakened four hours before admission by a sharp epigastric pain which two hours later centered about the right lower quadrant of the abdomen. He was nauseated and vomited and presented a considerable degree of pain and tenderness over McBurney's point with relative spasm in the right rectus muscle. He had a normal temperature and a leukocyte count of 12,000 with 86 per cent polymorphonuclear cells. He was operated on, but neither the appendix nor the cecum could be found. This patient had an uneventful recovery and was discharged on the ninth day after operation with a diagnosis of unrotated cecum.

There were 17 women who were submitted to operation for appendicitis primarily but who presented cystic ovaries, which were either punctured or wholly or partially removed. Their cases will be considered with the cases in which operation for appendicitis was performed.

Subtracting the 23 cases in which operation was not performed, the 20 cases of gynecologic conditions and the 1 case in which an appendix was not found from the total of 440 cases leaves to be reviewed a series of 396 cases of appendicitis in which operation was performed.

The records show what is indicated by most studies, that appendicitis is primarily a disease of young persons. Sixty-nine and four-tenths per cent of the patients ranged in age from 11 through 30. Eight and eight-tenths per cent were 10 or under. Forty-four and four-tenths per cent ranged from 11 through 20. Twenty-five per cent ranged from 21 through 30. Eight and five-tenths per cent were between 31 and 40. Five and five-tenths per cent were between 41 and 50. Four and two-tenths per cent were between 51 and 60. There were 1 per cent between

61 and 70 and 0.5 per cent between 71 and 75. The youngest patient was 3 years old and the oldest 75. The ages of 8 patients were not recorded.

There were 60.2 per cent women and girls and 39.8 per cent men and boys in the group. However, when only the patients with simple acute appendicitis, with a suppurative, gangrenous or ruptured appendix are considered, excluding those in whom the appendix showed no pathologic condition, was chronically diseased or was subacutely inflamed, there were 99 men and boys and 90 girls and women afflicted, or 10 per cent more of the former.

The average time that elapsed from the onset of the acute attacks in this series until hospitalization was thirty-four and eight-tenths hours, or approximately one and one-half days. While in some of the cases the time elapsed appeared too long, the average is better than that reported by M. Reid and others from Cincinnati,<sup>7</sup> in whose series the average time that elapsed from onset to hospitalization was ninety-one and two-tenths hours. It is significant to note that in the cases of ruptured appendixes in the series reported from Jameson Hospital the average time that elapsed from the onset of illness to hospitalization was sixty-two and two-tenths hours, or two and one-half days, a period almost twice as long as the average elapsed time in all the cases of acute appendicitis considered together. In those cases in which an abscess had formed before the patients' admission to the hospital, an average of one hundred and eight hours, or four and one-half days, had elapsed from the onset of symptoms. Cutting down this interval is one of the ways by which the physician and the patient can attack the problem of complicated appendicitis.

Stanton<sup>8</sup> has shown after a study of 16,424 cases from the literature that when operation is done during the first twenty-four hours of the attack the mortality in experienced hands is almost negligible. When it is done during the first half of the second day the average mortality is from 2 to 3 per cent. For cases in which operation is done after about forty hours the rate tends to rise sharply, so that when the intervention is done on the third day of the attack the operative mortality averages about 10 per cent. In general, operations done on the fourth or the fifth day are even more dangerous than those done on the third day. Beginning with interventions on the sixth day, the operative mortality starts to decline, and when the operation is done on the ninth or tenth day the rate corresponds approximately with that for the second day.

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7. Reid, M. R.; Poer, D. H., and Merrell, P.: A Statistical Study of 2,921 Cases of Appendicitis, *J. A. M. A.* **106**:665 (Feb. 29) 1936.

8. Stanton, E. M.: Acute Appendicitis, *Surg., Gynec. & Obst.* **59**:738 (Nov.) 1934.

Fifty-five per cent of the 396 patients submitted to operation stated that they had had previous attacks of appendicitis. When it is noted that in 29.1 per cent of the 189 cases of acute appendicitis in this series the appendix was gangrenous on admission and that in 63 per cent of these it had perforated, it would seem that too many persons are temporizing in the face of a fatal issue by neglecting first attacks.

Of the 396 cases in which operation was done for appendicitis, the condition was proved to be acute in 47 per cent, or 189 cases. In 41 per cent of this number the patients presented the so-called typical history of appendicitis in which there was pain in the epigastrium or about the umbilicus, followed by nausea, vomiting or both and later localized in the right lower quadrant of the abdomen.

Abdominal pain of some type was present in 100 per cent of the cases. Nausea or vomiting or both was associated with 74 per cent of the acute conditions and with less than 50 per cent of the nonacute. Tenderness in some degree was associated with 94 per cent of the acute conditions and with 92 per cent of the nonacute. Some degree of spasm in the right rectus muscle was associated with 62 per cent of the acute and with less than 30 per cent of the nonacute conditions.

Most authorities, it seems, agree that a rectal or pelvic examination is often helpful as an aid in the diagnosis of appendicitis, since tenderness, induration or mass might be presented to the palpating finger. This examination is said to be especially valuable in the case of children. In this series rectal examinations were recorded in only 32 instances, that is, in only 8.08 per cent of the total number of cases in which operation was done. It is interesting that of the rectal and vaginal examinations done 56 per cent gave positive findings, from tenderness to palpable masses. No doubt, many patients had had rectal and pelvic examinations before admission to the hospital, but these were not recorded. When it is not suitable to permit interns to make these examinations, the physicians in charge should be responsible for recording the facts ascertained by such procedures, in order that they may be a part of the completed records of the hospital.

In 17 per cent, or almost one fifth, of the total number of cases in which operation was done, the patient had taken some cathartic by mouth. A total of 69 patients took cathartics, while an additional 4 were given enemas before admission. Of the 9 patients who died, 6, or two thirds, had taken some cathartic by mouth. Fifteen patients with ruptured appendixes had had cathartics by mouth before admission, and a sixteenth had had an enema. Thus in 45 per cent of the cases in which rupture occurred the patients had had some type of intestinal cleansing before hospitalization. It is to be noted also that in 29 other cases of acute appendicitis, in 7 of which the appendixes were gangrenous, the patients had been given cathartics before admission. The figures indicate that 50 per cent of the purges were administered to 45 per cent



of the patients, among whom are included all those in whom the condition was acute and complicated. In the order of frequency the cathartics taken were: castor oil, liquid petrolatum, magnesia magma, magnesium sulfate, magnesium citrate, sal hepatica (a proprietary saline laxative) and mild mercurous chloride. In some instances the doctor who first saw the patient ordered the cathartic. Indeed medical practitioners should heed the present Reginald Fitz of Boston, who said: "Surely, in the early management of appendicitis to keep the bowels quiet should still be the first and last thought of the physician."<sup>9</sup>

The temperatures in the cases of simple acute appendicitis averaged 99.4 F., varying from 97.4 to 102.4 F. The pulse rates averaged 92, ranging from 74 to 122. The leukocyte counts averaged 9,435, varying between 6,450 and 27,900. The polymorphonuclear counts averaged 70.4 per cent, having a low of 56 and a high of 92.

In the cases of more serious involvement including instances of acute appendicitis with suppurative, gangrenous or ruptured appendixes, the temperatures averaged 101.8 F., with a range from 97 to 104.4 F., on admission. The pulse rates averaged 102, varying from 60 to 140. The leukocyte counts averaged 14,475, ranging from 8,100 to 24,650. The polymorphonuclear counts averaged 80 per cent, varying between 57 and 91.

Of the 396 cases in the series in which operation was done, the condition was acute in 189, as substantiated by pathologic diagnosis. Twenty-two of the cases were classified as instances of subacute involvement and 143 as cases of a chronic reaction, which means that infiltration of round cells and scarring or fibrosis had taken place in varying degrees as seen under the microscope. Forty-two appendixes were considered to be without pathologic manifestations. Thus, of the patients in this series, 48 per cent had acute appendicitis, 42 per cent had subacute or chronic appendicitis and 11 per cent had normal appendixes.

The cases of acute appendicitis may be subdivided as follows:

Simple acute .....	48, or 25%
Acute suppurative .....	86, or 46%
Acute gangrenous without rupture of appendix.....	20, or 11%
Acute gangrenous with rupture of appendix.....	30, or 19%

Among these cases of acute appendicitis, there were 11 instances of localized peritonitis, 12 instances of the formation of abscesses and 17 instances of spreading peritonitis.

There were 102 instances of discrepancy between the clinical and the microscopic diagnosis, that is, according to the pathologist, a 25 per cent error on the part of the surgeons. In 48 per cent of the cases in

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9. Fitz, R.: On Perforating Inflammation of the Vermiform Appendix with Special Reference to Its Early Diagnosis and Treatment, *New England J. Med.* **213**:245 (Aug. 8) 1935.

which these discrepancies occurred, the surgeon made a diagnosis of acute or subacute appendicitis when the pathologist could find only chronic lesions. In 7 per cent, the surgeon made a diagnosis of subacute or chronic appendicitis when the pathologist called the condition acute. In 24 per cent, the pathologist observed evidence of a pathologic condition when the surgeon had made a diagnosis of chronic or subacute appendicitis. In 20 per cent, the surgeon called the involvement acute when the pathologist saw no evidence of a pathologic condition.

The 396 cases of appendicitis in which operation was done in the hospital in 1935 and 1936 were managed by seventeen different surgeons. Of these, seven had 20 or more cases each, or 89 per cent of the total; five, from 2 to 14 each, or 9 per cent, and five, 1 each, or less than 2 per cent.

With reference to the surgical management in the cases studied, the rule has been to operate promptly when a diagnosis of acute appendicitis is made. When a condition is complicated by an appendical abscess, the tendency is to remove the appendix if possible and insert drains. The same procedure is followed in cases of acute perforative appendicitis with peritonitis. Drainage was employed in 17 per cent of all the cases in which operation was done. It appears that the right rectus incision is favored by the staff of this hospital, as it was used 234 times to 140 for the McBurney approach.

All the surgeons in this hospital favor the inversion of the stump of the appendix. This procedure was omitted only occasionally in the presence of an abscess and in some cases of peritonitis. In this connection Charles Mayo says:<sup>6</sup>

To invert or not to invert, that is the question. Most surgeons who invert do so that they may sleep more soundly, feeling that the danger of blowing out the stump has been obviated. There are four reasons why I do not invert the carbolyzed stump of the appendix. 1. Dr. Robertson of the section on Pathologic Anatomy at the Clinic has found that invariably, in cases in which appendectomy with inversion of the stump has been done in combination with some other surgical procedure and death has resulted, there is a pus pocket in the inverted stump up to twenty-one days postoperatively. 2. The cultured suture material used to invert the stump, once having run through the intestinal wall, invariably is infected with pathogenic bacteria. 3. Noninversion shortens the surgical procedure, and, fourthly, I have not had occasion to regret not having inverted the stump.

At the Jameson Hospital, chromic no. 1 suture material is generally used to close the abdominal wound. In the majority of cases the skin is closed with clips, and one or two silkworm gut stay sutures are used. In this series there is no record of any disruption of the abdominal wound while the patient has remained in the hospital. In this connection Carlucci<sup>10</sup> made a follow-up study of defects in abdominal wounds following appendectomy. Of 700 patients from Bellevue Hos-

10. Carlucci, G. A.: Abdominal-Wall Defects Following Appendectomy, *Ann. Surg.* 100:1177 (Dec.) 1934.

pital, 12 per cent had some degree of defect. A larger percentage of defects was noted in the cases in which approach was through a right rectus incision than in those in which a McBurney incision was used.

The stay in the hospital of the patients in the series ranged from four to one hundred and four days after operation, depending on such factors as the onset of complications, the use of drains and the initial severity of the condition. The average length of stay after operation was twelve and three-tenths days.

The following complications were present when the patients were admitted to the hospital or developed subsequently: There were 2 cases of pregnancy, in 1 of which abortion occurred on the fourth day after operation. There were complications of the chest in 6 cases (fibrinous pleurisy in 1, bronchopneumonia in 3, bilateral lobar pneumonia in 1 and empyema in 1). In 4 of these 6 cases the patients had received general anesthesia (nitrous oxide, oxygen and ether in 3 and nitrous oxide, oxygen and ethylene in 1), and in 2, spinal anesthesia (procaine hydrochloride). There was postoperative infection of the wound in 8 cases, pelvic abscess in 2, thrombophlebitis in 2, pyelitis in 1, cystitis in 1, fecal fistula in 1, pulmonary infarction in 1, otitis media of the left ear in 1, tonsillitis in 2, an abscessed tooth in 1 and infection of the upper part of the respiratory tract in 3. There were 13 patients whose temperature was above 101 F. later than the sixth day after operation, for reasons either not discovered or not recorded. Thus in 11 per cent of the cases in which operation was done there were complications of some sort caused by conditions other than the appendicitis.

Three hundred and seventy-seven patients received general anesthesia, usually with gas-oxygen induction followed by drop ether. A few were anesthetized by gas and oxygen alone or in conjunction with ether vapor. The gas was usually nitrous oxide, but ethylene was frequently used. One patient was given avertin (tribromethanol) supplemented by nitrous oxide and oxygen. Two patients were operated on under local anesthesia produced by procaine hydrochloride. Spinal anesthesia by procaine hydrochloride was used 16 times, or in only 4 per cent of the cases. No deaths attributable to anesthesia occurred.

In the two year period of 1935 and 1936, as has been pointed out, 440 patients were dismissed from the hospital with a diagnosis of appendicitis. The mortality for this whole group was 2.5 per cent. The mortality of 8.6 per cent which occurred in the group of 20 cases in which no operation was done has been discussed earlier in this paper. It was further noted that no deaths occurred among those patients whose appendectomies were only incidental to some other procedure. Of the 396 patients submitted to operation, 9 died, giving a mortality of 2.3 per cent for this group. This rate compares favorably with Davis'

figure of 2.92 per cent in the Providence Hospital in Detroit,<sup>11</sup> with Schullinger's rate of 5.08 per cent from the Presbyterian Hospital in New York,<sup>12</sup> and with Reid's rate of 6.3 per cent from the Cincinnati General Hospital.<sup>7</sup>

The records show that none of the cases with a fatal outcome were among those in which the condition was classified as uncomplicated. In other words, the mortality was zero in the combined cases of non-pathologic, chronic, subacute or simple acute involvement. If the remaining cases, of more severe involvement, are considered, the mortality becomes 6.3 per cent. Of the patients with acute suppurative conditions complicated by appendical abscess, bilateral lobar pneumonia developed in 1, and death occurred on the fourth day after operation; the mortality was thus 1.2 per cent in this group.

The remaining 8 patients who died were all from the group that had an acute gangrenous condition with ruptured appendix, the mortality for this group being 23 per cent. It may also be added that each one of these 8 had spreading peritonitis. Two of them were under a physician's care from the onset of symptoms, but because the initial symptoms were atypical the correct diagnosis was made too late. In all of these cases operation was done promptly after the patient's admission to the hospital, except in 1 in which the diagnosis was not made until an exploratory operation was done, thirty-six hours after admission.

In 17 instances of acute appendicitis with spreading peritonitis 8 of the patients died; the mortality in this group was thus 47 per cent. This compares unfavorably with rates from similar groups, such as 17.02 per cent reported by Schullinger<sup>12</sup> and 16.6 per cent reported by Arnheim and Neuhof.<sup>13</sup> It is to be pointed out, however, that 2 of the patients with diffuse peritonitis who died had other complications. One died on the fifth day after operation, with complicating bronchopneumonia; the other died on the sixty-fourth day, having suffered from a subhepatic abscess and empyema.

#### SUMMARY AND CONCLUSION

One of every 20 patients with a diagnosis of appendicitis was not operated on.

In 1 of every 25 patients appendicitis was incidental to other disturbances.

Seven of every 10 patients were 30 or younger.

11. Davis, J. E.; Muske, P. H.; Mulligan, P. L., and Gutov, J.: *Appendicitis*, J. A. M. A. **108**:1498 (May 1) 1937.

12. Schullinger, R. M.: *Acute Appendicitis and Associated Lesions*, Arch. Surg. **32**:65 (Jan.) 1936.

13. Arnheim, E. E., and Neuhof, H.: *Mortality in Appendicitis*, Surg., Gynec. & Obst. **59**:189 (Aug.) 1934.

There were more women with appendicitis than men, but a higher percentage of men had more serious forms of appendicitis.

The average time of thirty-four and eight-tenths hours from onset of symptoms to hospitalization is too long for the best management of appendicitis.

Too many persons go through first attacks of appendicitis without operative intervention.

Only 4 of every 10 patients presented histories typical of appendicitis.

Rectal examinations are important and should be recorded more frequently.

Too many patients receive cathartics for abdominal upsets which turn out to be appendicitis.

One fifth of the patients on whom operation was performed and two thirds of those who died had received cathartics, sometimes administered by the attending physician.

Approximately 5 of every 10 patients had acute appendicitis; 4 of every 10 had subacute or chronic appendicitis, and 1 of every 10 had a normal appendix.

Approximately 1 of every 5 patients whose condition was acute had a gangrenous appendix that had ruptured.

In approximately 1 of every 10 patients with acute involvement the condition was complicated with abscess or peritonitis.

The surgeon and the pathologist disagreed on diagnosis in 1 of every 4 cases.

The usual practice is to operate as soon as a diagnosis of acute appendicitis is made.

Incision is usually made through the right rectus muscle.

The stump of the appendix is inverted whenever this procedure is at all possible.

The average stay in the hospital is twelve and three-tenths days after operation.

In practically 1 out of every 10 cases the condition was complicated by something other than appendicitis.

Gas (nitrous oxide or ethylene), oxygen and drop ether are the usual anesthetics.

The mortality for the patients who were operated on was a small fraction over 2 of every 100.

The mortality for patients with acute gangrenous appendicitis with rupture was a fraction over 2 of every 10.

Death occurred in nearly 5 of every 10 patients with spreading peritonitis.

In view of this high mortality among patients with diffuse peritonitis, perhaps more attention should be given to the problem of devising some other plan of management for these patients. For example, operation might be deferred, as suggested by Arnheim and others.<sup>13</sup>

# MODIFIED DOUBLE ENTEROSTOMY (MIKULICZ) IN RADICAL SURGICAL TREATMENT OF INTUSSUSCEPTION IN CHILDREN

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DURHAM, N. C.

The high mortality following the resection of gangrenous or irreducible intussusception in infants and young children furnishes sufficient reason for a determined and continuous effort to attain an optimal technic. For the treatment of such a lesion a great many surgical methods have been employed. They may be briefly noted as: (1) resection with lateral or end to end anastomosis; (2) resection with double enterostomy (von Mikulicz,<sup>1</sup> Paul,<sup>2</sup> Hartmann<sup>3</sup>); (3) resection of the intussusceptum through an incision in the intussusciens, with or without lateral anastomosis (Barker,<sup>4</sup> Jessett,<sup>5</sup> Maunsell,<sup>6</sup> Coffey<sup>7</sup>); (4) lateral anastomosis about the lesion with secondary resection; (5) ileostomy with secondary resection; (6) lateral anastomosis about the lesion with secondary sloughing or healing (Rutherford,<sup>8</sup> Parry,<sup>9</sup> Montgomery and Mussil<sup>10</sup>); (7) enterectomy of the base of invagination or simple suture after mesenteric ligation, followed by spontaneous

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Dr. Dean Lewis has previously advocated the procedure recorded in this paper, stressing particularly the control of intestinal obstruction and the protection from extensive fluid loss gained by its use. The recent appearance of two consecutive cases in which treatment by this method was successful has stimulated this more detailed report.

1. von Mikulicz, J.: *Chirurgische Erfahrungen ueber das Darmcarcinom*, Arch. f. klin. Chir. **69**:28-47, 1903.

2. Paul, F. T.: Two Cases of Colectomy, Brit. M. J. **1**:245-246, 1900.

3. Hartmann, H.: *Travaux de chirurgie anatomo-cliniques*, Paris, G. Steinheil, 1907.

4. Barker, A. E.: A Suggestion for the Treatment of Irreducible Intussusception of the Bowels, Lancet **1**:79-81, 1892.

5. Jessett, F. B.: A Suggestion for the Treatment of Irreducible Intussusception of the Bowels, Lancet **1**:223, 1892.

6. Maunsell, H. W.: A New Method of Intestinal Surgery, Am. J. M. Sc. **103**:245-257, 1892.

7. Coffey, R. E.: Intestinal Intussusception, Ann. Surg. **45**:42-48, 1907.

8. Rutherford, H.: Irreducible Intussusception in the Infant Treated by Ileocolic Anastomosis, Brit. J. Child. Dis. **6**:405-410, 1909.

9. Parry, R. H.: The Treatment of Irreducible Intussusception by Lateral Anastomosis, Proc. Roy. Soc. Med. **2**:271-274, 1908-1909.

10. Montgomery, A. H., and Mussil, J. J.: The Treatment of Irreducible Intussusception in Children, Surg., Gynec. & Obst. **51**:415-419, 1930.

sloughing (Oderfeldt,<sup>11</sup> Capelle<sup>12</sup>); (8) incision in the wall of the intussusciens to permit manual reduction, followed by one of the aforementioned methods if necessary (Brown<sup>13</sup>). Statistics summarized from various clinics and from various individual reports show the appalling mortality of 70 per cent in 417 cases in which the patients were treated by one type or another of the foregoing operative procedures.

The optimal surgical technic for the treatment of irreducible or gangrenous intussusception occurring in early life should insure the following essential points: (1) rapidity of execution; (2) complete removal of the irreducible or gangrenous bowel; (3) control of the concomitant intestinal obstruction; (4) control of the loss of fluid, and (5) restoration of the continuity of the intestinal canal. Any discussion of these requirements in relation to the majority of the operative procedures outlined is outside the range of my experience. However, among 76 cases of intussusception in which the condition occurred in infants 2 years of age and under and in which the patients were treated in the surgical service of the Johns Hopkins Hospital there have been 6 instances in which resection has been indicated and performed. In all of the operations but 1, a resection of the ileum with end to end anastomosis, immediate resection followed by double enterostomy was the procedure of choice. Of the 6 patients, 3 died—a mortality of 50 per cent. It is the purpose of this paper to record my experience with the Mikulicz type of resection and to discuss in detail a modification in operative technic followed in the two most recent consecutive and successful resections.

#### REPORT OF CASES

CASE 1.—C. B., a white boy aged 10 months, was admitted to the Harriet Lane Home on Jan. 26, 1937, with a history of vomiting, abdominal pain and bloody stools. His illness had begun seventy-two hours previously. His birth, feeding and early development had been normal. He had had pertussis in April 1936 and had had frequent infections of the upper respiratory tract since that time, culminating in pneumonia and bilateral otitis media four weeks prior to this admission.

Seventy-two hours before admission the infant refused his afternoon feeding, and shortly thereafter he vomited. That evening he began to suffer from intermittent cramplike abdominal pain; it came on at hourly intervals and caused him to scream and clutch the side of his crib. He vomited throughout the night, and on the morning of the second day he was given an enema that returned with fecal material mixed with bright red blood. Attacks of pain and vomiting persisted, but they did not appear to be so frequent during the day as they had been

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11. Oderfeldt, H., cited by Bickham, W. S.: *Operative Surgery*, Philadelphia, W. B. Saunders Company, 1924, p. 774.

12. Capelle, W.: *Vorschlag einer einfachen und radikalen Operationsmethode bei Darminvagination*, *Deutsche Ztschr. f. Chir.* **243**:745-748, 1934.

13. Brown, H. P., Jr.: *Acute Intussusception in Children*, *Ann. Surg.* **81**:637-645, 1925.

during the preceding night. A physician reported normal abdominal findings on physical examination and prescribed castor oil. The child's symptoms became much worse. His mother noticed that he was voiding infrequently. On the day before admission a mass was thought to be palpable in the right lower abdominal quadrant. During the day the child continued to vomit and had four massive bloody stools. With the appearance of a fifth bloody stool on the following morning, hospitalization was advised.

On admission the child's temperature was 98 F., his pulse rate was 140 and his respiratory rate was 28. The white blood count was 12,000, and the hemoglobin content was 96 per cent. The infant was well nourished but dehydrated and washed out, lying quietly on the examining table and unresponsive to painful or noisy stimuli. The skin was dry, with a lemon yellow tinge. The cheeks were flushed, and the lips were cyanotic. The pharynx was sticky and injected. The abdominal wall was soft and relaxed, with evidence of intra-abdominal distention. There was a readily palpable mass extending from the right lower quadrant of the abdomen to the costal margin on the right side and thence across to the midepigastrium. It was sausage shaped, firm and rubbery and was perhaps 4 cm. in its greatest diameter. Palpation elicited no particular pain response from the child. The mass could not be felt by rectum, but the examining finger was smeared with blood. Physical examination otherwise gave negative results. The clinical impression was intussusception, of sixty to seventy-two hours' duration, and pharyngitis.

The infant was seen by the surgical consultant and was given 150 cc. of a 5 per cent solution of dextrose intravenously. Samples of his blood were grouped and matched for transfusion, and he was sent to the operating room for an immediate laparotomy.

*Operation.*—The operation consisted of resection of an irreducible and gangrenous intussusception and a double enterostomy with lateral anastomosis.

After anesthesia had been induced with ether by the drop method, the child's abdomen was cleaned with a 3.5 per cent solution of iodine followed by 70 per cent alcohol and was draped in the usual fashion. A long midright rectus incision was made. When the peritoneum was opened, many dilated loops of small intestine presented. A mass could be felt in the right side of the abdominal cavity. With some difficulty, this was brought out into the operative wound for inspection. It consisted of an ileocecal intussusception extending to the middle of the transverse colon. The portion of the large bowel at the ring and the entering ileum were bluish black, dull and obviously gangrenous. Tentative attempts to reduce the intussusception manually by milking the distal end of the mass were futile. Resection was commenced by cutting across the ileum, with the actual cautery between crushing clamps, at a point 8 cm. from the beginning of the intussusception. The mesentery of the ileum was divided between Kelly clamps. The cecum and the ascending colon were quite mobile, and after incision of the lateral peritoneum the mass was easily retracted mesially, exposing the mesentery of the large bowel. This was clamped and divided. Division of the transverse colon in its midportion completed the resection. The mesenteric vessels were ligated with no. 1 plain catgut sutures. The ends of the bowel, with clamps attached, were exteriorized in the upper angle of the incision, the colonic stoma being uppermost. At the suggestion of Dr. Dean Lewis, an ileocolic lateral anastomosis was performed at a point 8 cm. from the resected ends of the bowel, an outer layer of continuous fine black silk and an inner layer of no. 1 plain catgut being used. The upper peritoneal angle was closed about the exteriorized bowel with interrupted sutures of no. 1 plain catgut. The remainder of the peritoneum was closed



with a continuous suture of similar material. Four stay sutures of braided silk were laid. The fascial sheath was closed with interrupted figure-of-eight sutures of no. 0 chromic catgut. The edges of the skin were approximated with interrupted sutures of fine black silk.

*Postoperative Course.*—The child was given a transfusion immediately after the operation with 100 cc. of citrated blood, and a continuous intravenous "drip" of 5 per cent dextrose solution and 1.5 per cent saline solution was started. During the evening he vomited, and continuous gastric lavage was instituted. On the following day his condition rapidly improved, and the gastric siphonage was discontinued. On the third day after the operation water by mouth was given. This was followed by vomiting and by increasing abdominal distention, which became so alarming that the ileostomy was opened. Earlier in the day two stools had been passed by rectum. Relief from distention and from vomiting was immediate, and on the following day feeding by mouth was resumed. The parenteral intake of fluids was discontinued. During the next ten days the status quo was maintained, with drainage from the ileostomy and normal stools about equally divided in amount. The ends of the bowel could have been closed at any time, but this step was deferred because of the presence of an infection in the operative wound. Sixteen days after the operation bronchitis and bilateral otitis media developed. Loss of fluid through the ileostomy increased, the child's weight began to decrease, and his condition became progressively more critical. After twenty-four hours of parenteral intake of fluid the ends of the bowel were inverted with interrupted sutures of fine no. 1 catgut and the skin edges were approximated with silk sutures above the inverted bowel. The improvement after this procedure was dramatic, and the child was discharged on the twenty-eighth day after the operation.

*Pathologic Diagnosis.*—The diagnosis was ileocecal intussusception with necrosis of bowel.

CASE 2.—G. S., a white boy aged 7 months, was admitted to the Harriet Lane Home for Invalid Children on March 17, 1937. The admission note by Dr. William C. Stifler, Jr., of the resident staff, reads as follows: "The patient is a 7 month old white boy, who is admitted to the hospital because of vomiting and the passing of blood by rectum during the past thirty hours. The family history is non-contributory. The mother's labor was difficult, and the delivery of the child was by version and extraction. The neonatal period was normal. The feeding and the intake of vitamins have been fairly adequate. The development has been normal, and the baby has always been well except for a few colds, otitis media a few weeks ago and, since birth, a slight tendency toward constipation, for which he has been given castoria (an aqueous extract of senna with aromatics). Thirty hours before admission, at 6:30 a. m. yesterday, the child became ill very suddenly. He looked sick, whined as if in pain, vomited frequently and began passing by rectum material which apparently consisted of slime and blood, but no fecal material. He was given small amounts of milk and rather large amounts of water and continued to vomit. The vomiting has occurred two or three times every hour, has been unrelated to the milk and water taken by mouth, has been usually projectile, and has been watery and not stained green or brown. The baby has rested in bed very quietly, has whined and has had apparent attacks of pain, has slept little and has continued to look sicker and sicker. Today he has vomited every few minutes. There have been eleven passages of blood and slime by rectum, but no fecal material. No flatus has been observed. A physician was called yesterday morning and again later in the day. He attributed the

blood to straining and said he felt a mass in the abdomen, for which he advised an enema. The enema produced only blood. The physician called again this morning and advised that the parents bring the baby to the hospital.

"The temperature is 99.6 F.; the pulse rate is 160; the respiratory rate is 30. The blood count shows: hemoglobin, 101 per cent; red blood cells, 4,800,000; white blood cells, 11,700.

"Physical examination shows a sick-looking baby who lies very still, cries occasionally, and pays little attention to what is going on about him. He has a washed-out appearance around the eyes. He responds to external stimuli but does not resist examination at all. The breathing is rapid, but there is no cough. The skin is a trifle inelastic but is otherwise normal. The mucous membranes are of good color. There is no cyanosis. The glands are not enlarged. The head and the eyes are entirely normal. Both the ear drums are dull, but not bulging.

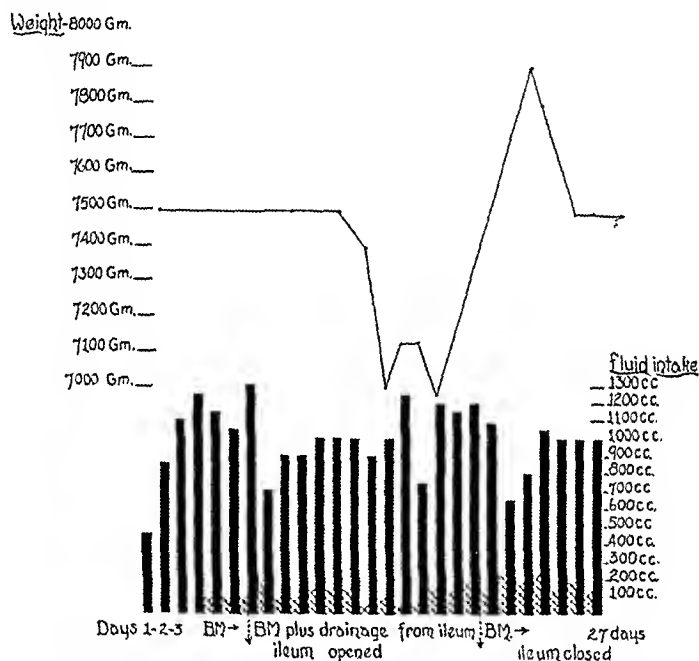


Fig. 1.—Control of fluid loss after resection by modified double enterostomy technic (case 1). Compare with chart 2.

The nose is clear. The mouth and the pharynx show no unusual conditions. The chest is normally developed. The lungs seem clear at percussion and auscultation. The heart is normal; the sounds are of good quality, and no murmurs are heard. The pulse is rapid but well sustained. The abdomen is not distended, is soft and is not tender. Just below the umbilicus and slightly to the left of the midline a mass can be seen and felt. It is about the size of a peach, is fairly firm and is slightly movable. The baby does not seem to object to palpation. On rectal examination one can feel the mass very plainly, and also a depression in the center, which feels like a cervix. No blood is present on the examining finger. The genitalia are normal. The joints and extremities are normal. Neurologic examination was not done.

"Impression: Intussusception, with the ileum far down in the colon, and probably with gangrene of the intestines."

The baby was seen by the surgical consultant and an immediate laparotomy was advised. While the operating room was being prepared, the baby was given 150 cc. of a 5 per cent dextrose solution intravenously and specimens of his blood were grouped for transfusion.

*Operation.*—The operation consisted of the resection of a gangrenous intussusception and a double enterostomy, with lateral anastomosis.

With the child under anesthesia, obtained with ether by the drop method, the entire abdomen was prepared with a 3.5 per cent solution of iodine and a 70 per cent solution of alcohol and was draped in the usual manner. A long right rectus incision was made. When the peritoneum was opened, the intussusception was at once visible. It was a typical ileocecal intussusception, involving the entire large bowel to the rectosigmoid junction. Reduction was started by gently milking the mass from below and was successfully carried out until the last segment

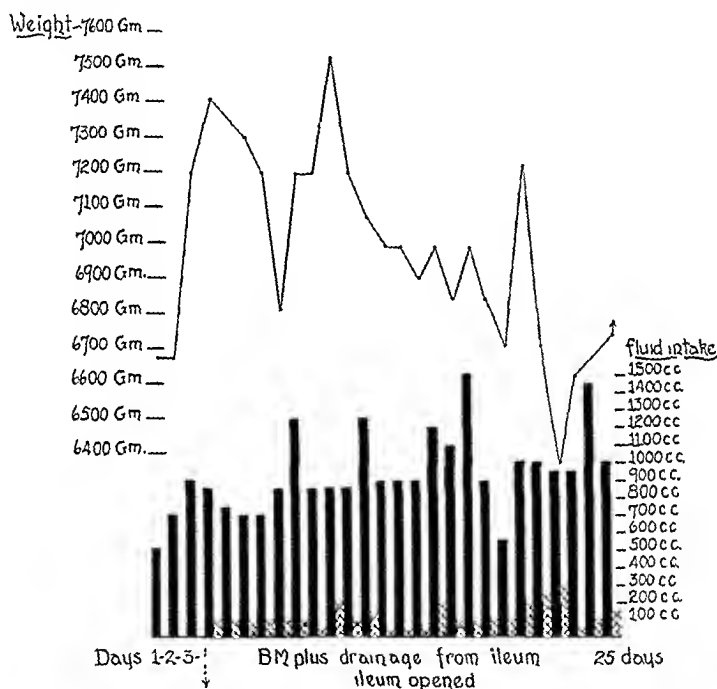


Fig. 2.—Early variation in fluid loss following resection with double enterostomy and failure to restore bowel continuity, recurrent over a period of nine months.

was reached. At this point even considerable pressure produced nothing but numerous rents in the serosa. The anterior wall of the intussusciens was incised longitudinally through the constricting ring, in the manner described by Brown. The mass was then forcibly reduced. The distal ileum was obviously gangrenous, and the necrotic area included a portion of the wall of the cecum and the appendix. The distal ileum at a point 10 cm. from the ileocecal valve was cut across with the actual cautery between crushing clamps. Its mesentery was clamped and divided. The peritoneum along the lateral abdominal wall was incised, and the cecum and the ascending colon were retracted mesially. There was an unusually long and mobile cecal mesentery. The mesenteric vessels to the large bowel were clamped and divided. The colon was resected between crushing clamps at a point just distal to the hepatic flexure. In addition to the gangrenous areas

noted, the wall of the entire ascending colon and cecum was edematous, friable and cyanotic. The bowel ends, with clamps attached, were then exteriorized in the upper angle of the incision for a distance of 2 to 3 cm., the colon being uppermost. In accordance with Dr. Dean Lewis' advice as noted in the report of the preceding case, a lateral ileocolic anastomosis was then performed at a point 8 cm. from the ends of the bowel. The usual outer layer of continuous fine black silk was used, followed by an inner layer of continuous no. 1 plain catgut. The upper angle of the peritoneal incision was closed about the double enterostomy with interrupted no. 1 plain catgut sutures and the remainder of the incision was closed with continuous no. 1 plain catgut sutures. Four stay sutures of braided silk were laid. The fascial sheath was closed with interrupted sutures of no. 0 chronic catgut and the skin with interrupted fine silk sutures. The stay sutures were tied over a roll of plain gauze.

The condition of the patient, which was very poor at the beginning of the operation, did not seem to be further affected by the procedure. The operating time was extended to forty minutes because of the prolonged efforts made to reduce the intussusception manually.

*Postoperative Course.*—The baby was given 120 cc. of a 5 per cent solution of dextrose and 80 cc. of citrated blood before leaving the operating room. On his return to the ward a continuous intravenous "drip" of 5 per cent dextrose solution and 1.5 per cent saline solution was instituted. Twenty-four hours after the operation moderate distention with vomiting occurred. It was controlled by gastric lavage, and it was not deemed necessary to open the ileostomy. Feeding was commenced on the third day after the operation, and was taken hungrily. The parenteral intake of fluids was discontinued. Stools appeared by rectum on the second day after the operation, and on the tenth day, with the patient under light anesthesia (ether again being used) the ends of the bowel were inverted with interrupted no. 1 plain catgut sutures, and the edges of the skin were approximated with interrupted fine silk sutures. The incision healed per primam, and the child was discharged as well on the twenty-eighth day after the operation.

*Pathologic Diagnosis.*—The diagnosis was ileocecal intussusception, with necrosis of the intestine.

#### COMMENT

The surgical principle of exteriorization of bowel with immediate or subsequent resection and formation of an abdominal fecal opening was established by the work of Mikulicz<sup>1</sup> in Germany, of Paul<sup>2</sup> in England and of Hartmann<sup>3</sup> in France. The value of the procedure lies in its rapidity of execution and in its prevention of intra-abdominal infection, particularly in the operative attack on tumors of the large bowel, where it has found its sphere of greatest usefulness. Restoration of continuity to the lumen of the bowel depends on obliteration of the spur resulting from the formation of the "gunbarrel" or double enterostomy, and this obliteration may at times offer some difficulty. In order to obviate this technical criticism, Hartmann<sup>3</sup> and Bloodgood<sup>14</sup> early reported having performed the Mikulicz resection with

14. Bloodgood, J. C.: Intestinal Obstruction Due to Volvulus or Adhesions of the Sigmoid Colon, and a Study of the Etiological Factors, *Ann. Surg.* **49**: 161-182, 1909.

immediate closure of the bowel ends and with the addition of lateral anastomosis. This modified Mikulicz resection has also been advised by Bier<sup>15</sup> in his *System of Surgery* for the treatment of sigmoid tumors. As far as can be ascertained, this modification of the Mikulicz resection has not been used previously in the radical treatment of gangrenous or irreducible intussusception in children.

From my experience with the successful operations recorded, this modification of the Mikulicz resection appears to fulfil adequately the requirements for the optimal surgical technic. It may not, of course,

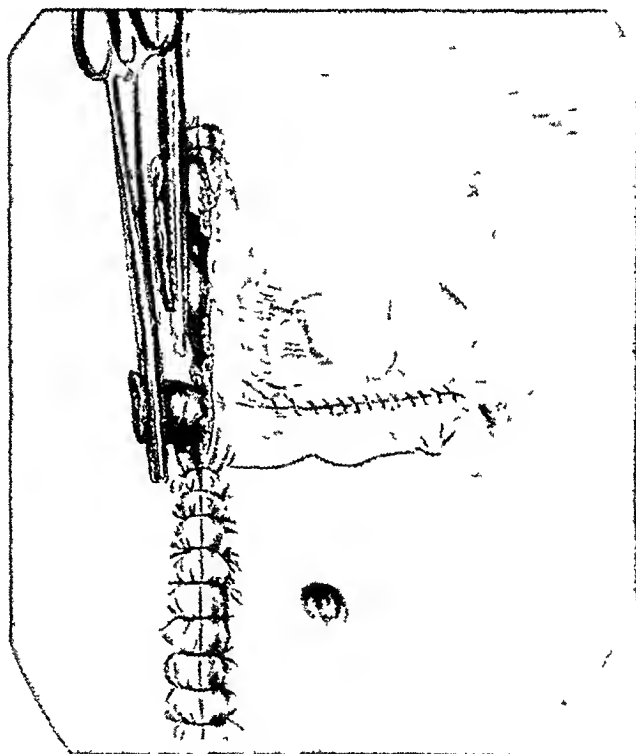


Fig. 3—Simple operative technic of modified double enterostomy.

be applicable to all cases of irreducible or gangrenous intussusception, but it appears indicated in all but those of agonal character or those in which final reduction may be obtained by Brown's maneuver. Operative periods of thirty and forty minutes from incision to final dressing indicate that the lateral anastomosis adds little to the time consumed in the performance of a simple Mikulicz resection. Possible absorption from a "side-tracked" intussusception or from bowel left on the abdominal wall is of course eliminated by primary removal of the involved intestine.

15. Bier, A ; Braun, H, and Kümmell, H : *Chirurgische Operationslehre* : II. Brustkorb und Bauch, Leipzig. J. Barth, 1912, p 604.

Worthy of special note is the fact that an ileostomy may be performed above the original point of obstruction if needed. In the first case reported, progressive distention and vomiting promptly subsided following removal of the clamps from the ileal stoma and drainage of the distended small bowel. In the second case an ileostomy was not necessary, and both ends of the bowel were inverted after the need of such drainage had passed, with primary healing.

The fourth and fifth requirements of an optimal method of resection demand control of the loss of fluid and restoration of continuity of the bowel. It is well known that infants are particularly susceptible to the effects of loss of fluid from an ileostomy or from diarrhea. The fluctuating and dangerous state of fluid balance, with concomitant electrolyte imbalance, is graphically illustrated in chart 2, in which is shown the constant loss of intestinal fluid through a simple double enterostomy. Chart 1 (case 1), by contrast, indicates the rapid and permanent control of fluid balance by closure of the ileostomy, followed by primary healing. The lateral anastomosis is effective immediately after the operation and functions as an ileocecal junction as soon as the ends of the bowel are inverted. Fluoroscopic and roentgenographic study of the 2 infants by means of barium enemas, six months and four months after operation respectively, showed obliteration of the inverted or "blind" bowel ends and an unobstructed stoma between the small and the large intestine that presented the roentgenographic picture of an end to end anastomosis.

#### SUMMARY

Resection, or a similar radical method, for the treatment of irreducible or gangrenous intussusception occurring in early life has a mortality of 70 per cent. In the two most recent consecutive and successful resections in the Johns Hopkins Hospital, the usual Mikulicz procedure has been modified by the addition of a lateral anastomosis. In addition to guaranteeing immediate continuity of the lumen of the bowel this technical modification has proved distinctly valuable in controlling the resultant intestinal obstruction and fluid loss.

# TOTAL BILE ACID-CHOLESTEROL RATIO IN HUMAN AND IN CANINE BILE

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The mechanism of the precipitation of cholesterol from bile to form gallstones has received increasing attention in recent years. Since the solubility of cholesterol in bile is dependent, to a great extent, on the presence of bile salts, considerable investigation has been directed toward the bile salt-cholesterol ratio in gallbladder bile. Experimental work on dogs clearly demonstrated that the wall of the inflamed gallbladder absorbs the bile salts of the contents rapidly, leaving an increased concentration of cholesterol.<sup>1</sup> A large number of studies of bile removed from the gallbladder either at operation<sup>1</sup> or at autopsy<sup>2</sup> in cases of disease of the bladder indicated that with the increasing inflammation of the organ the bile salt-cholesterol ratio was progressively lowered. This lowered ratio was obviously due to the decreased concentration of bile salts.

The methods employed by these various investigators for the determination of bile salts were either the Gregory-Pascoe procedure, which is specific for cholic acid only, or the Schmidt-Dart method, which measures only the conjugated bile acids. The investigations of

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From the Surgical Service of Dr. Ralph Colp and the Laboratories of Mount Sinai Hospital.

1. (a) Rosenthal, F., and Licht, H.: Die Resorption der Gallensäuren in der normalen und entzündeten Gallenblase, *Klin. Wchnschr.* **7**:1952, 1928. (b) Andrews, E.; Schoenheimer, R., and Hrdina, L.: Chemical Factors and the Role of the Gall Bladder: Etiology of Gall Stones, *Arch. Surg.* **25**:796 (Oct.) 1932. (c) Johnston, C. G.; Ravdin, I. S.; Riegel, C., and Allison, C. L.: Studies on Gall Bladder Function: IX. The Anion-Cation Content of Bile from the Normal and Infected Gall Bladder, *J. Clin. Investigation* **12**:67, 1933. (d) Riegel, C.; Ravdin, I. S.; Johnston, C. G., and Morrison, P. J.: Studies of Gall Bladder Function: XIII. The Composition of Gall Bladder and Calculi in Gall Bladder Disease, *Surg., Gynec. & Obst.* **62**:933-936. (e) Reinhold, J. G.; Ferguson, L. K., and Hunsberger, A., Jr.: The Composition of Human Gall Bladder Bile and Its Relationship to Cholelithiasis, *J. Clin. Investigation* **16**:367, 1937.

2. Newman, C. E.: Beitrag zum Studium der Gallenniederschlags- und Gallensteinbildung, *Beitr. z. path. Anat. u. z. allg. Path.* **86**:187, 1931.

Wieland and Revery<sup>3</sup> and our own determinations<sup>4</sup> demonstrated the presence of large amounts of desoxycholic acid in human bile. The Schmidt-Dart method was shown to be often fallacious, since by it about 20 per cent of free bile acids could be demonstrated to be present in normal bile while in pathologic bile the results often showed a high ratio due to the presence of an alcohol-soluble material containing amino-nitrogen. Consequently, the bile salt-cholesterol ratio obtained by these methods tends to be inaccurate. Marked qualitative differences occur in pathologic bile, for occasionally cholic acid is absent from the bile while at other times only free bile acids are present. These factors tend to nullify relative figures representing the bile salt-cholesterol ratio. Reinhold and his co-workers,<sup>1</sup> who have carefully limited themselves in their work to the determination of the cholate-cholesterol ratio, have clearly indicated the difficulty of determining the true bile salt-cholesterol ratio.

Spanner and Bauman<sup>5</sup> showed that the solubility of cholesterol is about four times as great in a 3 per cent solution of the sodium salt of desoxycholic acid as in one of the sodium salt of cholic acid. This faculty of desoxycholic acid to hold cholesterol in solution seems to be dependent on its ability to form addition compounds with cholesterol.<sup>6</sup> Therefore, the determination solely of the amount of cholic acid in the bile appears to be of minor importance in evaluating the factors which keep cholesterol in solution.

A series of bile acid and cholesterol analyses were made of a large number of specimens of bile from the gallbladder and from common duct fistulas to ascertain the fundamental factors determining the solubility of cholesterol in bile. Advantage was taken of a method which determined in each sample of bile the amount of cholic acid, of desoxycholic acid and of total bile acids as well as the content of conjugated bile acids and of free bile acids.<sup>7</sup> It was felt that a more accurate picture of the true bile acid-cholesterol ratio would be obtained as a result. In addition, for purposes of comparison with previous reports,

3. Wieland, H., and Revery, G.: Untersuchungen über die Gallensäuren: XXI. Zur Kenntnis der menschlichen Galle, *Ztschr. f. physiol. Chem.* **140**:186, 1924.

4. (a) Colp, R., and Doubilet, H.: Differential Analysis of Bile Acids in Human Gallbladder Bile, *Arch. Surg.* **33**:913 (Dec.) 1936. (b) Doubilet, H., and Colp, R.: Differential Analysis of Bile Acids in Human Bile from Fistulas, *ibid.* **34**:149 (Jan.) 1937.

5. Spanner, G. O., and Bauman, L.: The Behaviour of Cholesterol and Other Bile Constituents in Solutions of Bile Salts, *J. Biol. Chem.* **98**:181, 1932.

6. Wieland, H., and Sorge, H.: Untersuchungen über die Gallensäuren, *Ztschr. f. physiol. Chem.* **97**:1, 1916. Andrews, Schoenheimer and Hrdina.<sup>1b</sup>

7. Doubilet, H.: Differential Quantitative Bile Acid Analysis in Bile and in Duodenal Drainage, *J. Biol. Chem.* **114**:289, 1936.



the cholic acid-cholesterol ratio (Gregory-Pascoe method) as well as the conjugated bile acid-cholesterol ratio (Schmidt-Dart method) was estimated.

#### PROCEDURE

The specimens of bile were obtained either from the gallbladder at operation (by aspiration) or from hepatic fistulas drained daily after the operation. In the latter cases the amount needed in making the determinations was taken from the whole twenty-four hour collection. The amounts of cholic acid, desoxycholic acid, total bile acids and conjugated bile acids were determined by a method previously described.<sup>7</sup> The amount of cholesterol was estimated by the method of Elman and Taussig.<sup>8</sup>

Two hundred and ninety-one analyses were made. These may be classified as follows according to the source of the bile examined.

##### A. Gallbladder Bile.

1. Bile collected from apparently normal human gallbladders. In addition to 3 specimens of bile obtained at operation, there were 2 specimens of "B" bile obtained by duodenal tube and 1 specimen obtained at autopsy immediately after death (6 analyses).
2. Gallbladder bile obtained in cases of carcinoma of the pancreas (13 analyses).
3. Gallbladder bile obtained at the time of operation in cases of chronic cholecystitis (diagnosis proved pathologically). The gallbladders were divided into two subgroups:
  - (a) Gallbladders visualized after the injection of tetraiodophenolphthalein (21 analyses).
  - (b) Gallbladders not visualized by means of tetraiodophenolphthalein (10 analyses).
4. Gallbladder bile obtained in cases of acute cholecystitis:
  - (a) Early acute cholecystitis (10 analyses).
  - (b) Hydrops of the gallbladder (7 analyses).
5. Gallbladder bile obtained in cases of pathologic conditions of the liver (8 analyses).

##### B. Bile Obtained Postoperatively from Fistula Drainage.

6. Hepatic bile obtained in cases of carcinoma of the pancreas (2 cases; 6 analyses) and of miliary tuberculosis (1 case; 2 analyses).
7. Hepatic bile obtained in cases of calculous cholecystitis associated with choledocholithiasis (13 cases; 39 analyses).
8. Hepatic bile obtained in cases of stricture of the choledochus, operation being performed eight months after the primary cholecystectomy (1 case; 7 analyses).
9. Hepatic bile obtained in cases of acute pancreatitis (3 cases; 16 analyses).
10. Hepatic bile obtained in cases of different types of hepatitis and cholangitis (8 cases; 42 analyses).
11. Hepatic bile obtained after administration of bile salts (2 cases; 46 analyses).

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8. Elman, R., and Taussig, J. B.: The Quantitative Determination of Cholesterol in Bile, *J. Lab. & Clin. Med.* **17**:274, 1931.

12. Hepatic bile obtained to determine the effect on the bile acid-cholesterol ratio of variations in diet (1 case; 7 analyses).

C. Canine Bile.

13. Gallbladder bile obtained from dogs (8 analyses).

14. Hepatic bile (McMaster fistula) obtained from dogs (2 dogs; 43 analyses).

### RESULTS

*Bile from Gallbladders Normal in Appearance.*—Three analyses were made in cases in which no evidence of disease of the gallbladder or liver was present either at operation or in the subsequent clinical course (table 1). In addition the analyses are presented of 2 samples

TABLE 1.—*Bile from Gallbladders Normal in Appearance.*

Case	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio				Comment
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	
32	0.400	3.33	4.33	7.66	6.16	8.3	10.8	19.1	15.4	Recurrent attacks of epigastric pain; no pathologic condition
71	0.606	2.75	5.59	8.34	7.80	4.1	8.1	12.5	11.7	Symptoms relieved by appendectomy
108	0.229	1.53	5.96	7.54	4.43	7.0	26.0	23.0	19.5	Symptoms relieved by appendectomy
G.	0.156	1.41	1.16	2.57	....	9.0	7.4	16.4	....	"B" bile by duodenal tube; gallbladder normal by roentgen visualization
M.	0.243	1.09	2.39	3.43	....	4.5	9.9	14.4	....	"B" bile by duodenal tube; gallbladder normal by roentgen visualization
P.	0.266	1.89	4.31	6.20	0.33	7.1	16.2	16.2	1.2	Bile obtained 3 hr. after death following colonic resection
Average ratio.....						6.6	13.1	19.7	12.2	

of "B" bile obtained from patients who had no clinical or roentgenologic evidence of disease of the gallbladder. One analysis of gallbladder bile obtained soon after death is also presented. These analyses are presented to give some idea of the composition of normal bile. The average total bile acid-cholesterol ratio was found to be 19.7. The normal bile acid-cholesterol ratio is probably close to 20, as was evidenced subsequently by the examination of hepatic bile.

*Gallbladder Bile Obtained in Cases of Carcinoma of the Pancreas with Complete Obstruction.*—The first 8 analyses of bile obtained from patients with complete obstruction in an early stage gave an average ratio of total bile acids to cholesterol of 23.9. The last 5 analyses were on bile obtained from patients in whom prolonged obstruction had caused an absorption of the greater part of the bile salts and pigment

(the early stage of "white bile"). The total bile acid-cholesterol ratio was 188, only a slight decrease from that in the first group. The average figure, then, for the total bile acid-cholesterol ratio is 21.6, agreeing closely with the figures given in table 1 for the bile acid-cholesterol ratio in bile from normal gallbladders.

*Gallbladder Bile Obtained in Cases of Chronic and Acute Cholecystitis.*—In the cases in which the gallbladder was visualized after the injection of tetraiodophenolphthalein, the average total bile acid-cholesterol ratio was found to be 13 (table 3). The fact that the dye could enter the gallbladder and be concentrated sufficiently for visuali-

TABLE 2—*Gallbladder Bile Obtained in Cases of Carcinoma of the Pancreas with Obstruction*

Case	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio			
		Cholic Acid	Desoxy- cholic Acid	Total Bile Acids	Conju- gated Bile Acids	Cholic Acid	Desoxy- cholic Acid	Total Bile Acids	Conju- gated Bile Acids
Early obstruction									
U	0.068	0.87	1.16	2.03	0.83	12.8	17.0	29.8	12.2
E R	0.097	1.70	1.40	3.10	2.66 <sup>9</sup>	17.6	14.4	32.0	27.4
38	0.600	4.25	5.50	9.75	8.86	7.1	9.1	16.2	14.7
86	0.352	3.63	2.53	6.16	5.92	10.3	7.2	17.5	17.0
116	0.066	6.13	6.89	13.02	6.82	9.2	10.3	19.5	10.2
122	0.096	1.70	1.40	3.10	2.66	17.7	14.6	32.3	27.7
135	0.519	4.55	6.63	11.18	3.63	8.7	12.8	21.5	7.0
136	0.494	6.74	4.60	11.34	7.41	13.6	9.3	22.9	15.0
Average	0.360	3.7	3.8	7.46	4.85	12.1	11.8	23.9	16.4
Advanced obstruction:									
55	0.003	0.03	0.11	0.14	0.12	10.0	36.6	46.6	40.0
127	0.003	0.015	0.11	0.125	0.15	1.9	13.7	15.6	28.7
137	0.026	0.09	0.02	0.11	0.19	3.5	0.8	4.3	7.3
141	0.106	0.26	0.22	0.48	0.57	2.4	2.1	4.5	5.4
144	0.074	0.95	0.37	1.32	1.00	13.0	5.0	18.0	13.5
Average	0.040	0.27	0.17	0.43	0.40	6.2	12.6	18.8	17.0
Total average	0.240	2.4	2.4	4.8	2.9	9.8	11.8	21.6	16.6

zation indicated that the gallbladder was functioning, that is, that it could fill and empty itself and could concentrate the bile fairly well. The cholesterol concentrations averaged 0.540 per cent. This is rather high when compared with the concentration of 0.360 per cent obtained in cases of early obstruction (table 2). The bile acid concentration, of 4.96 per cent, was lower than that which has been reported as normal.<sup>9</sup> An important question was raised: Had the bile acids been partially absorbed by the chronically inflamed gallbladder wall, or was the hepatic bile lower in bile acid concentration when it entered the gallbladder?

Bile obtained in cases in which the gallbladder was not visualized after the oral administration of dye (table 4) was found to have a total

9. Hammarsten, O: A Text-Book of Physiological Chemistry, New York, J. Wiley & Sons, 1906, p. 275.

bile acid-cholesterol ratio of 7.7. This is definitely lower than the values found when physiologic function of the gallbladder was preserved. The average cholesterol content in this group was 0.452 per

TABLE 3.—*Gallbladder Bile Obtained in Cases of Chronic Cholecystitis (Gallbladders Visualized After Injection of Tetraiodophenolphthalein)*

Case	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio			
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
40.....	0.732	3.33	7.02	10.45	7.41	4.5	9.6	14.1	10.1
41.....	1.500	0.61	1.81	2.42	2.39	0.4	1.2	1.6	1.5
44.....	0.155	1.31	4.89	6.20	1.38	8.3	31.0	39.3	8.8
64.....	0.441	1.58	1.58	5.24	1.77	3.6	8.3	11.9	4.0
79.....	1.320	1.93	1.93	7.36	5.52	1.4	4.1	5.5	4.2
83.....	0.217	1.41	1.41	3.57	3.23	6.4	10.0	16.4	14.9
84.....	0.022	0.12	0.12	0.47	0.22	5.4	16.0	21.4	1.41
93.....	0.533	1.99	5.07	7.06	5.05	2.4	6.1	8.5	6.0
99.....	0.148	0.86	0.63	1.49	2.34	5.8	4.2	10.0	16.0
102.....	0.769	2.78	6.33	9.01	5.33	3.6	8.3	11.9	7.0
103.....	0.764	1.31	5.96	7.27	3.73	1.7	7.8	9.5	4.8
117.....	0.227	1.10	1.16	2.26	0.20	4.9	5.1	10.0	0.9
124.....	0.484	2.26	6.40	8.66	5.77	4.7	13.2	17.9	12.0
128.....	0.735	2.90	8.71	11.61	6.79	3.9	11.8	15.7	9.2
129.....	0.422	0.62	3.06	3.68	1.85	1.4	7.2	8.6	4.6
134.....	0.056	0.10	0.64	0.74	0.06	1.8	11.4	13.2	1.0
138.....	0.392	1.22	5.11	6.33	3.75	3.1	13.0	16.1	9.5
145.....	0.851	1.74	2.26	4.00	3.50	2.0	2.7	4.7	4.1
147.....	0.312	1.87	2.13	4.00	3.01	6.0	7.0	13.0	9.6
148.....	0.377	1.88	3.62	4.50	....	2.3	9.6	12.0	...
S. K.....	0.613	1.75	2.72	4.47	1.31	3.4	5.2	8.7	2.5
Average.....	0.540	1.51	3.45	4.96	3.24	3.7	9.3	13.0	7.2

TABLE 4.—*Gallbladder Bile Obtained in Cases of Chronic Cholecystitis (Nonvisualized Gallbladders)*

Case	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio			
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
41.....	0.038	0.22	0.35	0.57	0.42	3.8	6.0	9.8	7.2
47.....	0.581	1.82	4.48	6.30	4.62	3.1	7.7	10.8	7.9
48.....	0.845	2.20	4.74	6.94	1.96	2.6	5.6	8.2	2.3
65A.....	0.540	1.37	2.84	4.21	3.00	2.6	5.2	7.8	3.5
88.....	0.663	1.94	2.80	4.74	4.16	2.9	4.2	7.1	6.2
89.....	0.463	0.91	2.24	3.15	3.04	2.0	4.8	6.8	6.6
118.....	0.178	0.50	0.58	1.08	....	2.8	3.2	6.0	...
130.....	0.126	0.71	0.64	1.35	0.51	3.6	5.1	10.7	6.4
146.....	0.412	1.20	1.64	2.84	2.79	2.9	4.0	6.9	6.7
C. C.....	0.655	0.73	1.39	2.12	1.38	1.1	2.1	3.2	2.1
Average.....	0.452	1.16	2.17	3.33	2.22	2.9	4.8	7.7	5.7

cent, slightly lower than in the cases reported in table 3 (0.540 per cent). The decrease in the amount of total bile acids, however, brought the ratio down to 7.7.

In cases of acute cholecystitis (table 5) the total bile acid-cholesterol ratio was found to average 6, slightly lower than in cases of advanced

chronic cholecystitis. The figures for cholesterol gave an average of 0.546 per cent, and those for the total bile acids an average of 2.15 per cent. These figures seem to indicate that in acute cholecystitis the lowered bile acid concentration is due to a rapid selective absorption of bile acids, which leaves behind a relatively increased concentration of cholesterol

TABLE 5—*Gallbladder Bile Obtained in Cases of Acute Cholecystitis*

Case	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio			
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
34	0.080	0.14	0.34	0.48	1.15	1.7	4.2	5.9	14.4
35	0.105	0.12	0.93	1.05	0.99	1.1	8.8	9.9	9.4
81	0.877	0.73	1.39	2.12	1.26	0.8	1.6	2.4	1.4
90	0.789	1.25	7.09	8.34	7.03	1.0	9.0	10.6	8.9
111	0.506	0.18	0.12	0.30	0.03	0.3	0.2	0.5	0.03
120	0.470	0	0.50	0.50	0	0	1.0	0	0
125	0.126	0.57	1.35	1.95	0.76	4.5	10.9	15.4	6.0
130	0.155	0.36	0.91	1.27	0.69	2.3	5.8	8.1	4.4
143	1.625	0.08	0.61	0.69	0.64	0.04	0.5	0.54	0.4
151	0.750	1.58	3.05	4.63	5.58	2.1	4.1	6.2	7.4
Average	0.546	0.5	1.65	2.15	1.81	1.4	4.6	6.0	5.2

TABLE 6—*Gallbladder Bile Obtained in Cases of Hydrops of the Gallbladder*

Case	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio			
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
66	0.016	0	0	0	0	0	0	0	0
82	0.012	0	0	0	0	0	0	0	0
119	0.500	0	0	0	0.52	0	0	0	1.0
121	0.272	0	0	0	0.23	0	0	0	0.8
132	0.063	0	0	0	0.34	0	0	0	5.4
149	0.003	0	0	0	0	0	0	0	0
150	0.067	0	0	0	0	0	0	0	0
Average	0.133	0	0	0	0.15	0	0	0	1.0

Table 6 presents the analyses made in 7 cases of hydrops of the gallbladder. These results apparently indicate that a fairly large concentration of cholesterol remains after the bile acids have been completely absorbed. The cholesterol content may be very high. Thus, in case 119 the cholesterol concentration was 0.500 per cent. A number of analyses of the protein content of the hydropic fluid indicated that high cholesterol content was usually associated with a high protein concentration. In cases in which the contents of the gallbladder were thin and watery, as in case 149, the cholesterol concentration was very low. Although neither cholic nor desoxycholic acid could be detected, analysis

by the Schmidt-Dart method for conjugated bile acids occasionally yielded positive results, due to the presence in pathologic bile of an alcohol-soluble material yielding aminonitrogen.<sup>4</sup>

*Gallbladder Bile Obtained in Cases of Disease of the Liver.*—This series of 8 analyses (table 7) indicates that after severe hepatic injury the excretion of cholesterol tends to be very low. The gallbladder bile in the case of B, in which diagnosis of acute hepatitis was made on the basis of biopsy of material from the liver, was found to have a

TABLE 7.—*Gallbladder Bile Obtained in Cases of Disease of the Liver*

Case	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio				Comment
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	
B.	0.055	1.24	5.07	6.31	0.33	22.5	91.3	113.8	6.0	Acute hepatitis
S.	0.017	0.13	0.76	0.89	0.40	7.7	44.7	52.4	23.5	Bile obtained at autopsy from patient with cirrhosis of liver who died in cholemia
131	0.030	0.60	2.30	2.90	1.20	20.0	77.0	97.0	40.0	Normal gallbladder; large liver; fever; hepatitis (?)
133	0.235	3.70	5.25	8.95	3.05	15.7	22.3	38.0	21.5	Jaundice; swollen liver with precipitated pigment in bile ducts; serous hepatitis (?)
105	0.073	1.65	2.23	3.88	2.75	22.6	30.5	52.1	37.7	Operation after acute pain in right upper quadrant and fever; thin-walled gallbladder containing stones
31	0.015	0.15	0.05	0.20	0.52	10.0	3.3	13.3	34.7	Cholangitis; atonic gallbladder containing thin bile
40	0.034	0.22	0.35	0.57	0.36	6.5	10.3	16.8	10.6	Cholangitis; atonic gallbladder containing thin bile
46	0.015	0.04	0.81	0.85	0.26	2.6	54.0	56.6	17.3	Acute pancreatitis with biliary obstruction; normal gallbladder containing thin bile

high concentration of bile acids. The gallbladder, which was edematous and glassy in appearance, had evidently strongly concentrated the dark bile present. In spite of this, the cholesterol content was only 0.055 per cent, giving a total bile acid-cholesterol ratio of 113.8. The content of conjugated bile acids was typically low.<sup>4</sup> As a result, the conjugated bile acid-cholesterol ratio was only 6. In the case of S, bile was obtained immediately after death, the patient dying in cholemia. Although the total bile acid concentration was only 0.89 per cent, the cholesterol content was so low (0.017 per cent) that the ratio was 52.4. In case 131 an enlarged liver with an apparently normal biliary tract was found at operation. Unfortunately, biopsy of the liver was not done, so that the diagnosis of hepatitis was problematic. In case 133, that of a male

patient suffering from jaundice and pruritus, operation revealed an enlarged congested liver but a normal gallbladder. A biopsy of tissue from the liver revealed a morphologically normal parenchyma, but the fine bile ducts contained precipitated pigment. Subsequent studies with iodized poppyseed oil showed the entire biliary tract to be extremely narrowed. This may have been the result of swelling of the surrounding parenchyma, a condition described by Eppinger under the term "serous hepatitis." In this case the total bile acid-cholesterol ratio was 38. In case 155 operation was performed immediately after an attack of severe pain and tenderness in the right upper quadrant of the abdomen, accompanied by high fever. At operation a thin-walled non-inflamed gallbladder containing stones was found. The liver was enlarged. The total bile acid-cholesterol ratio was 52.1. In both case 31 and case 40, a large atonic gallbladder containing thin bile was found.

TABLE 8—*Hepatic Bile Obtained in Cases of Noncalculous Disease*

Case	Day After Operation	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio				Comment
			Cholic Acid	Desoxy cholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxy cholic Acid	Total Bile Acids	Conjugated Bile Acids	
57	15th	0.033	0.26	0.22	0.48	0.39	7.9	6.3	14.2	11.8	Carcinoma of pancreas
	17th	0.036	0.24	0.22	0.46	0.39	6.7	6.1	12.8	11.1	
121	2d	0.005	0.04	0.11	0.15	0	8.0	22.0	30.0	0	Carcinoma of pancreas
	3d	0.006	0.01	0.05	0.06	0.06	1.7	8.3	10.0	10.0	
	6th	0.016	0.03	0.07	0.10	0	0.8	4.4	6.2	0	
	20th	0.023	0.12	0.35	0.46	0.26	5.2	15.2	20.4	11.3	
52	15th	0.029	0.20	0.52	0.72	0.55	6.9	17.9	24.8	18.9	Miliary tuberculosis
	19th	0.020	0.14	0.72	0.86	0.46	7.0	36.0	43.0	23.0	

In these 2 cases biopsy of the liver showed considerable pericholangitic cellular infiltration and fibrosis. Both the cholesterol and the bile acid concentration were low, giving a ratio of 13.3 and 16.8 respectively. In case 46 operation was performed for sudden biliary obstruction due to acute pancreatitis. The gallbladder, containing thin bile, appeared normal. The total bile acid-cholesterol ratio was 56.6, owing to the very low concentration of cholesterol. These results suggest that when severe injury of the liver has occurred, as a result of inflammation, of degeneration or of acute obstruction, the cholesterol concentration of the gallbladder bile tends to be extremely low.

*Hepatic Bile Obtained in Cases of Noncalculous Disease.*—Three analyses were made in cases in which hepatic drainage was carried out for noncalculous disease (table 8). In case 57 and in case 121 drainage was done for carcinoma of the pancreas with obstruction. The patient in case 52, after an operation for acute pain in the right upper quadrant of the abdomen associated with high fever, was found to have miliary tuberculosis. In case 57 the total bile acid-cholesterol ratio was found

to be 14.2 and 12.8 on the fifteenth and the seventeenth day respectively. In case 121 the bile gave a total bile acid-cholesterol ratio of 30 immediately after the release of obstruction, but on the twentieth day the ratio was 20.4. In case 52 the total bile acid-cholesterol ratio

TABLE 9.—*Hepatic Bile Obtained in Cases of Calculous Cholecystitis Associated with Cholelithiasis*

Case	Day After Operation	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio			
			Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
139	1st	0.101	0.05	0.04	0.09	0.25	0.5	0.4	0.9	2.4
	10th	0.075	0.23	0.09	0.37	0.49	3.7	1.2	4.9	6.5
	19th	0.094	0.28	0.57	0.84	0.54	2.9	6.1	9.0	5.7
	26th	0.133	0.24	0.64	0.88	0.72	1.8	4.8	6.6	5.4
S. B.	68th	0.079	0.27	0.19	0.46	0.73	3.4	2.4	5.8	9.2
111	10th	0.138	0.15	0.51	0.66	0.81	1.1	5.7	6.8	5.9
	12th	0.077	0.14	0.46	0.60	0.70	1.8	6.0	7.8	9.1
	13th	0.063	0.07	0.19	0.26	0.32	1.1	3.0	4.1	5.1
M. F.	3d	0.004	0.007	0.035	0.04	0.06	1.7	8.7	10.4	15.0
	6th	0.020	0.03	0.12	0.15	0.13	1.5	6.0	7.5	6.5
	13th	0.033	0.06	0.16	0.22	0.27	1.1	3.0	4.1	5.1
	29th	0.013	0.01	0.13	0.14	0.16	0.7	10.0	10.7	10.7
J. J.	1st	0.092	0.19	0.67	0.86	0.36	2.1	7.3	9.4	3.9
	5th	0.052	0.07	0.21	0.28	0.26	0.8	2.6	3.4	3.2
	13th	0.076	0.09	0.30	0.39	0.22	1.2	4.0	5.2	5.1
M. K.	8th	0.076	0.27	0.30	0.57	0.37	3.5	3.9	7.4	7.5
S. M.	1st	0.035	0.05	0.37	0.42	0.13	1.4	10.6	12.0	3.7
	5th	0.137	0.50	1.25	1.15	0.92	3.6	9.1	12.7	6.7
	12th	0.125	0.38	0.72	1.10	0.45	3.0	5.8	8.8	3.6
	25th	0.057	0.52	1.24	1.76	0.81	9.1	21.8	30.9	14.2*
	35th	0.095	0.42	0.63	1.05	0.54	4.4	6.6	11.0	5.7
	41st	0.121	0.36	1.14	1.50	0.38	5.0	9.4	12.4	3.1
M. M.	12th	0.007	0.05	0.09	0.14	0.24	7.1	12.0	20.0	34.3
	21st	0.023	0.11	0.02	0.13	0.26	4.8	0.9	5.6	11.3
C. S.	1st	0.025	0.015	0.067	0.082	0.13	0.6	2.7	3.3	5.2
	9th	0.082	0.22	0.33	0.55	0.50	2.7	4.0	6.7	6.1
134	1st	0.090	0.10	0.57	0.67	0.07	1.1	6.3	7.4	0.8
	6th	0.012	0.09	0.42	0.51	0.41	2.1	10.0	12.1	9.7
	12th	0.077	0.05	0.29	0.34	0.05	0.6	3.8	4.4	0.6
S. S.	2d	0.034	0.01	0.04	0.05	0.16	1.2	1.2	2.4	4.7
	3d	0.019	0.035	0.001	0.036	0.11	1.8	0	1.8	1.6
H. S.	1st	0.011	0.15	0.82	0.97	0.23	13.6	74.5	88.1	20.9
	3d	0.022	0.09	0.66	0.75	0.27	4.1	30.0	34.1	12.5
	5th	0.036	0.10	0.14	0.24	0.32	2.8	3.9	6.7	8.9
	8th	0.033	0.03	0.50	0.53	0.32	6.9	15.1	16.0	9.7
	10th	0.021	0.04	0.28	0.32	0.18	1.9	13.3	15.2	8.6
28	1st	0.004	0.08	0.21	0.29	0.13	20.0	52.5	72.5	32.5
	5th	0.006	0.08	0	0.08	0	13.3	0	13.3	0
	9th	0.010	0.08	0.01	0.12	0	8.0	4.0	12.0	0
Average ratio.....							2.5	9.5	12.0	8.0

\* After administration of 4 Gm. of ox bile salt.

was 24.8 and 43 on the fifteenth and the seventeenth day respectively. The results are presented as ratios obtained in cases of noncalculous disease of the biliary tract. They indicate that the ratio after the patient's recovery from the obstruction probably approximates 20.

*Hepatic Bile Obtained in Cases of Calculous Cholecystitis Associated with Cholelithiasis.*—This group of 13 analyses (table 9) is pre-



sented in some detail. Repeated intermittent biliary obstruction has been shown to lead to impairment of hepatic function, with a resultant low bile acid concentration of the hepatic bile even after prolonged drainage.<sup>4</sup> As a result, the total bile acid-cholesterol ratio in the cases considered here was low. In some instances there was a tendency for the ratio to rise gradually after the obstruction had been released. Certain exceptions must be noted. When operation was performed immediately during an acute obstruction (case of H. S. and case 28), the drainage bile during the first few days gave a very high ratio (88.1 for H. S. and 72.5 in case 28), apparently as a result of hepatic injury due to acute back pressure on the liver. One other point may be noted. In the case of S. M., after the administration of 4 Gm. of ox bile salts the total bile acid-cholesterol ratio rose from 8.12 to 30.9.

TABLE 10.—*Hepatic Bile Obtained in a Case of Stricture of Choledochus Eight Months After Operation (Case T. R.)*

Day After Operation	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio			
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
1st	0.037	0.05	0.05	0.10	0.10	1.3	1.3	2.7	2.7
3d	0.022	0.06	0.14	0.20	0.80	2.7	6.4	9.1	36.4
4th	0.039	0.08	0.17	0.25	0.91	2.0	4.4	6.4	2.4
5th	0.034	0.09	0.24	0.33	0.29	2.6	7.1	9.7	8.5
7th	0.030	0.08	0.32	0.40	0.17	2.7	10.7	13.3	5.7
9th	0.077	0.12	0.55	0.67	0.27	1.6	7.1	8.7	2.5
16th	0.100	0.08	1.23	1.31	0.37	0.8	12.3	13.1	1.7

*Hepatic Bile Obtained in Cases of Stricture of the Choledochus.*—A patient (T. R., table 10) had an almost complete obstruction of the choledochus for eight months as a result of a stricture following a primary cholecystectomy. The analyses revealed the excretion of the different bile acids to be in abnormal proportions. The predominant features were: (1) almost total absence of cholic acid, (2) a high proportion of desoxycholic acid and (3) a low concentration of conjugated bile acids. As can be seen, the total bile acid-cholesterol ratio was 2.7 on the first day, but thereafter it showed an average of about 10.

*Hepatic Bile Obtained in Cases of Acute Pancreatitis.*—The results of analysis of bile in 3 cases of acute pancreatitis are presented in table 11. In each instance the total bile acid concentration after about the eighth day tended to be much higher than in the previously presented cases of choledocholithiasis (table 9). The cholesterol concentration, however, also tended to be high. As a result the total bile acid-cholesterol ratio was rather low, except in the drainage bile on the twelfth day in case 62.

TABLE 11.—*Hepatic Bile Obtained in Cases of Acute Pancreatitis*

Case	Day After Operation	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio			
			Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
G. K.	2d	0.055	0.07	0.08	0.15	0.26	1.2	1.4	2.6	4.7
	3d	0.032	0.04	0.05	0.09	0.13	1.2	1.6	2.8	4.1
	4th	0.041	0.07	0.01	0.08	0.26	1.7	0.2	1.9	6.3
	5th	0.079	0.50	0.50	0.80	1.12	3.3	6.3	9.6	14.2
	8th	0.176	0.50	0.82	1.82	1.05	2.9	4.6	7.5	6.0
	10th	0.147	0.39	0.55	1.24	1.06	2.0	5.8	7.8	7.7
S. Z.	1st	0.250	0.43	0.28	0.71	0.80	1.9	1.2	3.1	3.5
	2d	0.253	0.20	0.04	0.24	0.49	0.8	0.2	1.0	1.9
	3d	0.252	0.27	0.12	0.39	0.68	1.1	0.5	1.6	2.7
	4th	0.140	0.53	0.19	0.72	0.95	3.8	1.3	5.1	6.8
	6th	0.115	0.28	0.12	0.40	0.79	2.4	1.0	3.4	6.8
	12th	0.118	0.54	0.61	1.18	0.94	4.6	5.4	10.0	8.0
	19th	0.127	0.54	0.89	0.96	1.01	4.3	3.1	7.2	8.0
C2	2d	0.038	0.26	0.11	0.37	....	6.8	2.9	9.7	...
	5th	0.048	0.23	0.29	0.52	....	4.8	6.0	10.8	...
	12th	0.061	0.77	0.56	1.35	0.78	12.6	9.2	21.8	12.8

TABLE 12.—*Hepatic Bile Obtained in Cases of Hepatitis and Cholangitis*

Case	Day After Operation	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio				Comment
			Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	
F. F.	1st	0.002	0.45	0.10	0.55	0.65	225.0	50.0	275.0	325.0	Long history of epigastric pain; pruritus; jaundice; acute interstitial hepatitis
	2d										
	3d	0.059	0.17	0.06	0.23	0.05	1.9	0.6	2.6	0.8	
	5th	0.033	0.04	0.03	0.09	0.05	1.2	1.5	2.7	2.6	
	7th	0.003	0	0	0	0.27	0	0	0	90.0	
	9th	0.003	0.11	0.12	0.23	0.21	36.7	40.0	76.7	70.0	
	10th	0.002	0.13	0.35	0.51	0.32	65.0	190.0	255.0	100.0	
133	4th	0.003	0.07	0.07	0.14	0.03	23.3	23.3	46.6	10.0	Jaundice; pruritus; swollen liver; narrowed biliary tree; serous hepatitis (?)
	12th	0.004	0.06	0.10	0.16	0.16	15.0	25.0	40.0	40.0	
	19th	0.005	0.07	0.05	0.15	0.11	14.0	16.0	30.0	22.0	
	26th	0.006	0.06	0.10	0.16	0.35	10.0	16.6	26.6	58.3	
	34th	0.022	0.14	0.33	0.47	0.27	6.4	15.0	21.4	12.3	
	41st	0.021	0.06	0.13	0.19	0.26	2.0	6.2	9.1	12.3	
C. S.	2d	0.002	0	0.01	0.04	0	0	20.0	20.0	0	Acute cholangitis; pyclophlebitis; Diabetes
	3d	0.008	0	0.23	0.23	0	0	76.7	76.7	0	
	4th	0.005	0	0.04	0.04	0	0	8.0	8.0	0	
S. C.	1st	0.015	0.06	0.15	0.21	0.36	4.0	10.0	14.0	24.0	Acute cholangitis; parenchymatous degeneration
	3d										
	8th	0.013	0.01	0.08	0.04	0.10	0.77	2.3	3.1	7.7	
J. K.	1st	0.083	0.25	0.69	0.94	0.54	3.0	8.3	11.3	6.5	Marked jaundice and pruritus 12 years after cholecystectomy; chronic cholangitis; partial obstruction due to angulation of the drainage tube after the 80th day
	12th	0.046	0.08	0.18	0.26	0.33	1.7	3.0	5.6	7.2	
	16th	0.032	0.12	0.23	0.35	3.75	7.2	10.9	18.1	117.2	
	21st	0.024	0.17	0.26	0.43	0.29	7.1	10.8	17.9	12.1	
	26th	0.025	0.21	0.39	0.60	0.56	8.4	15.6	24.0	22.4	
	37th	0.020	0.28	0.31	0.59	0.62	14.0	15.5	29.5	31.0	
	48th	0.039	0.37	0.33	0.70	0.92	9.5	8.5	17.9	23.6	
	81st	0.006	0.11	1.09	1.20	0.71	18.3	181.7	200.0	118.3	
	88th	0.026	1.01	0.41	1.42	1.17	38.8	15.8	54.6	45.0	
	94th	0.053	0.30	0.06	0.36	0.58	5.4	1.1	6.5	10.5	
I. R.	8th	0.032	0	0.10	0.10	0	0	3.1	3.1	0	Acute hepatitis; edematous bile ducts and gallbladder; cholecystostomy
	12th	0.037	0.02	0.03	0.07	0.21	0.5	1.3	1.8	5.7	
E. S.	1st	0.006	0.04	0.16	0.20	0.08	6.7	26.7	33.3	13.3	Chronic cholecystitis and cholangitis; choledocholithiasis
	3d	0.017	0.04	0.31	0.35	0.22	2.3	18.2	20.6	12.9	
	10th	0.014	0.07	0.25	0.32	0.17	5.0	17.9	22.9	12.1	
F. J.	2d	0.053	0.05	0.07	0.12	0.17	0.9	1.3	2.3	3.2	Acute cholangitis; early carcinoma of right hepatic duct
	3d	0.023	0.02	0.24	0.26	0.09	0.9	1.7	2.6	3.9	
	4th	0.019	0.025	0.026	0.051	0.13	1.3	1.4	2.7	6.8	
	5th	0.023	0.04	0.02	0.06	0.21	1.7	0.9	2.6	9.3	
	7th	0.062	0.10	0.21	0.31	0.38	1.6	3.4	5.0	6.1	
	9th	0.047	0.13	0.36	0.49	0.51	2.8	7.7	10.4	10.8	
	13th	0.076	0.14	0.37	0.51	0.46	1.8	4.9	6.7	6.0	
	15th	0.079	0.17	0.18	0.35	1.07	2.2	2.3	4.4	13.6	
	35th	0.050	0.42	0.05	0.47	1.03	8.4	1.0	9.4	20.6	
	108th	0.085	0.29	0.29	0.58	1.19	3.4	3.4	6.8	14.0	

*Hepatic Bile Obtained in Cases of Hepatitis and Cholangitis.*—The analyses of hepatic bile made in 8 cases show the effect of injury to the liver on the excretion of cholesterol (table 12). The data can be correlated with the results of analyses of gallbladder bile obtained in cases of similar conditions (table 7). The high total bile acid-cholesterol ratio is especially to be noted in drainage bile obtained during the first few days in cases of hepatitis. In the case of F. F. the first two days' drainage gave a ratio of 275; in case 133 the ratio was 46.6 on the fourth day, and in the case of C. S. the ratio was 76.7 on the third day.

TABLE 13—*Bile Obtained After Administration of Bile Salts in a Case of Complete Fistula Following Carcinoma of the Pancreas (case 23)*

Date	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio				Bile Acid Administered
		Cholic Acid	Desoxy cholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxy cholic Acid	Total Bile Acids	Conjugated Bile Acids	
Sept 17	0.130	0.33	0.74	1.12	0.81	2.5	4.9	7.4	5.4	
18	0.129	0.47	0.61	1.08	0.96	3.6	4.7	8.3	7.5	
19	0.206	0.36	0.75	1.11	1.03	1.7	3.6	5.3	5.0	
20	0.173	0.25	1.19	1.44	1.42	1.4	6.9	8.3	8.2	15 Gm desoxy cholic
21	0.172	0.24	1.24	1.48	1.45	1.4	7.2	8.6	8.3	10 Gm desoxy cholic
22	0.121	0.13	1.66	1.79	1.82	1.1	13.7	14.8	15.0	15 Gm desoxy cholic
23	0.137	0.13	1.31	1.44	1.00	0.9	9.6	10.5	7.3	
24	0.128	0.70	0.38	1.08	0.92	5.5	3.0	8.5	7.2	
25	0.039	1.05	0.31	1.36	1.17	10.6	3.1	13.7	11.8	15 Gm cholic
26	0.077	0.89	0.62	1.51	1.28	11.5	8.0	19.5	16.6	15 Gm cholic
27	0.097	0.95	1.37	2.32	1.28	9.8	14.1	23.9	13.2	15 Gm cholic
28	0.112	0.95	1.13	2.18	1.11	8.5	10.1	18.6	10.0	
29	0.123	1.11	1.72	2.83	1.06	9.0	14.0	23.0	8.6	
30	0.112	1.07	1.34	2.41	0.95	9.6	11.0	20.6	8.5	
Oct 1	0.149	0.71	0.44	1.15	0.56	4.8	3.0	7.8	3.8	
2	0.128	0.45	0.51	0.96	0.59	3.5	4.0	7.5	4.6	

In cases of chronic and acute cholangitis the total bile acid-cholesterol ratio tends to be rather low (cases of J. K. and F. J.). When both cholangitis and hepatic degeneration were found, the ratio tended to be low (case S. C.). On the other hand, when acute obstruction was associated with cholangitis (as in the case of J. K. after the eightieth day of drainage, and in the case of E. S.), the ratio was high. In 1 case (that of I. R.) bile drained through an edematous and inflamed gallbladder. As a result, a large proportion of the bile acids was absorbed, apparently much more rapidly than the cholesterol. This resulted in a very low total bile acid-cholesterol ratio.

*Bile Obtained to Determine the Effect of Administration of Bile Salts.*—In the case of S. M. (table 9) it was noted that the total bile acid-cholesterol ratio was raised following the administration of 4 Gm. of ox bile salts. Similar effects were produced in 2 other cases reported here. In case 23 (table 13) large amounts of desoxycholic acid and

also of cholic acid were administered. The patient had a choledochal fistula as a result of obstruction due to carcinoma of the pancreas. The bile was reinjected daily by means of a small stomach tube. After the administration of desoxycholic acid the bile acid concentration rose. As a result, the bile acid-cholesterol ratio was raised. After the administration of cholic acid the cholesterol percentage rose somewhat, but the amount of total bile acids rose noticeably. As a result, the ratio was elevated during the period of administration of cholic acid. Sim-

TABLE 14.—*Bile Obtained After Administration of Bile Salts in a Case of Cholangitis and Carcinoma of the Right Hepatic Duct (Case of F. J.)*

Day After Operation	Chols- terol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio				Ox Bile Salts Admin- istered, Gm.
		Cholic Acid	Desoxy- cholic Acid	Total Bile Acids	Conju- gated Bile Acids	Cholic Acid	Desoxy- cholic Acid	Total Bile Acids	Conju- gated Bile Acids	
Second operation										
10th.....	0.007	0.01	0.32	0.33	0.01	1.4	45.7	47.1	5.7	4
20th.....	0.011	0.03	0.36	0.39	0.85	2.7	32.7	35.5	77.3	4
30th.....	0.013	0.03	0.09	0.12	0.27	2.3	6.9	9.2	20.8	
40th.....	0.011	0.02	0.31	0.33	0.25	1.8	28.2	30.0	22.7	4
42d.....	0.012	0.007	0.024	0.031	0.32	0.6	2.0	2.6	26.7	
44th.....	0.007	0.04	0.26	0.20	0.22	5.7	37.1	42.0	31.4	5
45th.....	0.003	0.07	0.46	0.53	0.05	23.3	133.3	176.7	16.7	5
46th.....	0.015	0.08	0.12	0.20	0.03	3.3	8.0	11.3	2.0	
47th.....	0.014	0.12	0.08	0.20	0.05	8.6	5.7	14.3	3.6	4
48th.....	0.012	0.09	0.14	0.23	0.02	7.5	11.5	19.2	1.7	1.3
49th.....	0.025	0.09	0.08	0.17	0	1.3	1.2	6.8	0	
51st.....	0.015	0.09	0.01	0.13	0.27	6.0	2.7	8.7	18.0	
52d.....	0.012	0.016	0.032	0.018	0.29	1.3	2.7	4.0	24.2	5
57th.....	0.032	0.07	0.78	0.85	0.20	2.2	21.4	26.6	6.2	5
58th.....	0.017	0.09	0.63	0.72	0.28	5.3	37.1	42.0	16.5	5
63d.....	0.021	0.07	0.52	0.59	0.10	3.3	24.8	28.1	4.8	5
65th.....	0.032	0.13	0.36	0.49	0.33	4.1	11.2	15.0	10.3	5
69th.....	0.026	0.11	0.60	0.71	0.38	4.2	23.1	27.3	14.6	5
74th.....	0.034	0.11	0.32	0.43	0.34	3.2	9.4	12.6	10.0	5
78th.....	0.024	0.15	0.51	0.66	0.49	6.2	21.3	27.5	20.4	5
84th.....	0.021	0.15	0.45	0.60	0.41	7.1	21.4	28.1	14.8	5
90th.....	0.020	0.17	0.42	0.59	0.23	8.5	21.0	29.5	11.5	5
95th.....	0.034	0.12	0.51	0.63	0.44	3.5	15.0	18.5	12.9	5
97th.....	0.033	0.19	0.61	0.80	0.57	5.8	18.5	24.2	16.7	5
112th.....	0.019	0.01	0.21	0.22	0.20	0.5	11.1	11.6	10.5	
115th.....	0.025	0.01	0.12	0.13	0.14	0.4	4.8	5.2	5.6	
147th.....	0.029	0.07	0.46	0.53	0.32	2.4	15.9	18.3	11.0	2
156th.....	0.033	0.12	0.53	0.65	0.26	3.6	16.1	19.7	7.9	2
184th.....	0.019	0.07	0.66	0.73	0.39	3.7	34.7	38.4	20.5	2
191st.....	0.013	0.04	0.28	0.32	0.22	3.1	21.5	24.6	16.9	2

ilar results were produced in a case of long-continued fistula resulting from the presence of cholangitis and a carcinoma of the right side of the liver (table 14). With each cessation of administration of bile salts, the ratio fell. Ox bile salts were administered in this case.

*Bile Obtained to Determine the Effect of Various Diets.*—An attempt was made to determine the influence of diet on the total bile acid-cholesterol ratio. In the case of a patient (M. F., table 15) who had been operated on for calculous cholecystitis and choledocholithiasis, an attempt was made to feed pure carbohydrate, pure protein and pure fat diets. Although these diets were somewhat disagreeable, the patient

took them for three day periods after he had completely recovered from the operation. Bile was collected over twenty-four hour periods, and equal quantities were pooled for three day periods. There was a daily loss of 300 to 500 cc. of bile through the fistula, but the loss of bile salts was partially made up by giving the patient 3 Gm. of ox bile salts every day. During the experimental period the cholesterol concentration gradually rose, but at the same time the bile acid concentration also rose, so that the total bile acid-cholesterol ratio did not vary with the different diets. The cholesterol concentration was highest during and after the taking of the fat diet, but the results, although suggestive, cannot be considered significant. It is of interest to note that after the

TABLE 15—*Bile Obtained to Test the Effect of Various Diets on the Bile Acid-Cholesterol Ratio (Case of M. F. Calculous Cholecystitis, Choledocholithiasis)*

Day After Operation	Cholesterol, %	Bile Acid Percentage			Bile Acid-Cholesterol Ratio			Diet for 3 Day Periods
		Cholic Acid	Desoxy-cholic Acid	Total Bile Acids	Cholic Acid	Desoxy-cholic Acid	Total Bile Acids	
20th .. ..	0.043	0.19	0.25	0.44	4.4	6.0	10.4	Hospital diet
22d, 23d, 24th..	0.073	0.21	0.18	0.39	3.0	2.5	5.5	High carbohydrate CHO, 700; P, 43; F, 3
25th, 26th, 27th	0.059	0.20	0.12	0.32	3.4	2.0	5.4	High protein CHO, 96; P, 244; F, 77
28th, 29th, 30th	0.111	0.36	0.27	0.63	3.2	2.4	5.6	High fat CHO, 18; P, 43; F, 300
31st, 32d, 33d	0.148	0.55	0.27	0.82	3.7	1.8	5.5	Hospital diet
34th, 35th	0.121	0.38	0.31	0.69	3.1	2.5	5.6	Hospital diet
40th .	0.095	0.56	0.40	0.96	5.9	4.1	10.0	Hospital diet; drainage after closure of tube for 5 days

fistula tube had been closed for five days, thus establishing a closed enterohepatic circulation of bile salts, the ratio rose to 10, and the bile acid concentration, although somewhat low, reached its highest point.

*Canine Gallbladder and Hepatic Bile.*—Since a great deal of investigative work has been done on canine bile, three tables are presented on the results of analyses of gallbladder bile and hepatic bile. Table 16 summarizes the results of 8 analyses of gallbladder bile. The average ratio was found to be 161 for cholic acid, 246 for total bile acids, and 135 for conjugated bile acids. Table 17 summarizes the results of analyses made during experiments on a dog with a McMaster fistula to which the bile was refed. The fistula was obstructed for a five day period and a ten day period by clamping the drainage tube. As can be seen, the total bile acid concentration tended to drop gradually after each period of obstruction. The cholesterol concentration tended to be

little influenced except immediately following the operation and immediately after the release of acute obstruction, when the cholesterol concentration was very low. As in the human being, the total bile salt-

TABLE 16.—*Gallbladder Bile from Dogs*

Case	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio			
		Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
65.....	0.108	7.51	6.01	13.52	8.56	68	56	123	70
74.....	0.072	8.48	3.50	11.98	10.75	118	46	161	135
X.....	0.055	11.94	2.50	14.24	7.81	217	42	259	142
P.....	0.054	4.28	6.18	10.46	4.11	79	114	191	77
79.....	0.054	9.97	8.50	18.47	9.04	185	157	342	167
76.....	0.080	9.14	8.53	17.97	7.58	114	110	225	95
31.....	0.055	10.67	5.29	15.96	7.39	194	96	290	134
75.....	0.033	10.37	2.12	12.49	8.18	314	61	378	248
Average.....	64	9.02	5.32	14.34	7.03	161	85	246	135

TABLE 17.—*Bile from Dog with Biliary Fistula; Bile Refed*

Dog 67:	Day After Operation	Cholesterol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio			
			Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Conjugated Bile Acids
	2d.....	0.004	0.8	0.7	1.6	2.0	190	215	405	400
	5th.....	0.008	1.5	2.4	3.9	2.9	184	301	485	360
	7th.....	0.013	2.7	1.6	4.3	3.4	207	125	331	263
	12th.....	0.011	2.7	1.9	4.6	3.0	243	173	416	274
	12th to 17th day, obstruction									
	19th.....	0.007	1.1	1.3	2.4	1.0	154	189	343	187
	20th.....	0.014	1.7	1.7	3.0	1.8	123	91	216	126
	21st.....	0.020	2.1	2.2	4.2	2.9	103	108	211	146
	23d.....	0.016	2.0	1.7	3.7	1.8	125	106	231	100
	26th.....	0.014	1.6	1.1	2.7	1.9	117	77	194	137
	28th.....	0.013	1.6	1.0	2.6	1.7	124	83	207	134
	28th to 33d day, obstruction									
	40th.....	0.006	1.1	1.8	2.9	1.3	188	293	482	213
	42d.....	0.007	1.8	0.8	2.6	2.2	263	114	377	316
	44th.....	0.014	1.6	1.3	2.9	1.9	117	90	207	136
	47th.....	0.009	1.4	0.7	2.2	1.5	161	80	241	172
	49th.....	0.008	1.8	0.5	2.2	1.8	222	59	281	227
	51st.....	0.006	0.9	1.3	1.0	1.4	143	225	368	225
	55th.....	0.005	1.0	0.2	1.2	1.4	202	40	242	280
	57th.....	0.006	1.4	0.7	2.1	1.0	232	120	352	263
	59th.....	0.003	1.6	0.6	2.3	1.9	204	79	283	239
	62d.....	0.011	1.7	0.3	2.1	1.8	159	29	188	264
	64th.....	0.004	0.8	0	0.8	0.8	202	5	207	137
	Average.....		1.5	1.1	2.6	1.9	174	125	298	218

cholesterol ratio was accordingly increased at these periods. The cholesterol concentration was so low and the variations so small that the figures cannot be considered significant.

Table 18 summarizes the results of feeding large quantities of various pure bile acids to a dog with a McMaster fistula. No bile was

refed. The results are similar to those in the human being in that the concentration of cholesterol was not significantly influenced by increasing the concentration of bile acids in the bile as a result of their administration. Consequently the total bile acid-cholesterol ratio tended to be definitely increased each time bile salts were administered. It is to be noted that only a trace of cholesterol was present in the bile after the administration of dehydrocholic acid. This result may have been due to the fact that cholesterol is insoluble in dehydrocholic acid.

TABLE 18.—*Bile Obtained After Administration of Bile Salts to Dog with McMaster Fistula*

Dog 79: Day After Opera- tion	Choles- terol, %	Bile Acid Percentage				Bile Acid-Cholesterol Ratio				Comment; Bile Acid Administration
		Cholic Acid	Desoxy- cholic Acid	Total Bile Acids	Conju- gated Bile Acids	Cholic Acid	Desoxy- cholic Acid	Total Bile Acids	Conju- gated Bile Acids	
4th	0.004	0.62	0.28	0.90	0.65	155	70	225	162	
8th	0.012	1.50	0.40	1.90	1.28	125	33	158	107	
12th	0.013	1.82	1.31	3.13	0.68	140	100	240	52	
16th	0.012	1.10	0.89	1.99	0.56	91	74	165	47	4 Gm. cholic
20th	0.007	0.34	1.39	1.73	0.48	49	108	247	68	(3 days)
24th	0.006	0.56	1.14	1.70	0.30	93	100	283	50	4 Gm. desoxy-
26th	0.008	0.36	1.75	2.11	0.30	45	218	253	37	cholic (3 days)
27th	0.010	1.01	1.72	2.73	0.98	101	172	273	98	8 Gm. desoxy-
29th	0.010	1.34	1.65	2.99	0.35	134	163	290	35	cholic (2 days)
31st	0.009	0.93	1.03	1.96	0.67	103	114	217	97	8 Gm. cholic
33d	0.011	1.64	1.91	3.55	1.50	149	173	322	130	(2 days)
34th	0.008	0.94	1.80	2.78	0.94	158	222	308	117	8 Gm. ox bile
36th	0.012	1.50	1.90	3.40	1.70	150	226	376	142	salts (2 days)
38th	0.015	1.90	1.90	3.80	1.23	100	126	226	82	8 Gm. ox bile
40th	0.012	1.90	1.52	3.42	1.90	126	226	352	158	salts (2 days)
45th	0.011	1.05	1.33	2.38	0.66	95	216	311	60	8 Gm. glyco-
47th	0.012	1.76	1.51	3.27	1.39	147	272	419	115	cholic (2 days)
49th	0.009	1.19	0.97	2.16	0.88	120	216	336	95	8 Gm. glyco-
51st	0.008	0.37	1.00	1.37	0.89	125	272	397	111	cholic (2 days)
53d	0.004	0.58	0.41	0.99	0.56	107	240	347	140	8 Gm. desoxy-
55th	0.001	0.22	0.71*	0.93	0.20	200	246	446	200	cholic (2 days)
56th	0.001	0.33	0.50*	0.83	0.52	102	247	349	140	6 Gm. dehydro-
						500*	830	1330	520	cholic (2 days)

\* Dehydrocholic acid (?).

#### COMMENT

The data on gallbladder bile obtained from normal gallbladders and in cases of carcinoma of the pancreas as well as from hepatic drainage after the tenth day following the operation suggest that the normal total bile acid-cholesterol ratio in human bile lies somewhere around 20. In cases of early chronic cholecystitis the total bile acid-cholesterol ratio was found to average 13. With more advanced cholecystitis the ratio fell to 7.7 and when acute cholecystitis was present the ratio was 6. The

ratios were of course much higher than those obtained by the Gregory-Pascoe (cholic acid) method, and they were somewhat higher than the ratios calculated from the results of the Schmidt-Dart method for bile acids (conjugated bile acids). Why was the bile acid-cholesterol ratio lowered? May it be inferred that the damaged gallbladder absorbed the bile acids more rapidly than the cholesterol and that this resulted in the lowering of the ratio? That such a course of events takes place with acute cholecystitis is strongly suggested both by previous experimental work<sup>6</sup> and by a comparison of the analyses presented here of the bile obtained from the two groups of chronically diseased functioning gallbladders (table 3) and of that obtained from acutely inflamed gallbladders (table 5). The average cholesterol concentration was almost exactly similar in the two groups (0.540 per cent and 0.546 per cent). The second group contained chronically diseased gallbladders which had become suddenly inflamed. Since the cholesterol concentrations were equal in the two groups, may we not infer that the bile acid concentrations were also similar just prior to the onset of inflammation and that the low bile acid content in the cases of acute inflammation was due to absorption of the acids?

However, another possible reason for the low bile acid-cholesterol ratio may be considered. The analyses of hepatic bile obtained in cases of chronic cholecystitis associated with choledocholithiasis indicate that the liver often secretes a rather low concentration of bile acids. The cholesterol concentration tends to be relatively high, however, and seems to be only partially influenced by the bile acid concentration. The gradually rising bile acid-cholesterol ratio after an operation seems to be due, in great part, to the increasing concentration in bile acids. The excretion of cholesterol tends to be fixed, although it is influenced to some extent by physical factors of solubility. The figures, then, suggest that the low bile acid-cholesterol ratio associated with chronic cholecystitis may possibly be due not to absorption of bile acids by the diseased gallbladder wall but to a diminished excretion of bile acids by the liver.

The bile acid-cholesterol ratio can be considered of importance only if the type of bile acid present is known. Cholesterol is about four times as soluble in a 3 per cent solution of sodium desoxycholate as in a solution of cholate. The saturation point of and the precipitation of cholesterol from bile will be determined by the type of bile acid present. According to Spanner and Bauman,<sup>5</sup> cholesterol (theoretically) will precipitate in cholic acid if the ratio falls below 80, while it will not precipitate in a desoxycholate solution until the ratio is below 20. Actually, in addition to the factor of simple solubility, cholesterol forms addition compounds with desoxycholic acid.<sup>6</sup> If a bile salt solution is shaken up with finely ground cholesterol for four hours and then care-



fully filtered, the desoxycholate-cholesterol ratio, 20, will be similar to that found by Spanner and Bauman<sup>5</sup> in a 3 per cent solution, and slightly lower in more concentrated solutions (table 19). If, however, sodium desoxycholate is dissolved in alcohol and excess cholesterol is added, addition compounds are formed. If this solution is dried, the residue redissolved in water and the excess cholesterol filtered off, the desoxycholate-cholesterol ratio will be found to be about 10. In other words, the danger of precipitation of cholesterol is no greater in a 1:80 solution of cholesterol in sodium cholate than in a 1:10 solution of cholesterol in sodium desoxycholate. In previous presentations<sup>4</sup> it was shown that with increasing degrees of cholecystitis the ratio of cholic acid to desoxycholic acid in the bile fell. Similar low ratios of cholic to desoxycholic acid were found in chronic cholangitis and also in prolonged intermittent biliary obstruction. It therefore follows that the total bile acid-cholesterol ratio is no indication of the degree of satura-

TABLE 19.—*Solubility of Cholesterol in Sodium Desoxycholate*

Percentage of Desoxycholate	Cholesterol Held in Solution After Mechanical Shaking		Cholesterol Held in Solution After Forming Addition Compound in Alcohol	
	Percentage	Ratio	Percentage	Ratio
2.0	0.085	23.5	0.156	12.8
4.0	0.240	16.6	0.400	10.0
5.0	0.476	16.8	0.770	10.4

tion of cholesterol in any one sample of bile. Since the amount of desoxycholic acid is relatively increased, a total bile acid-cholesterol ratio of 10 in bile from a patient with chronic cholecystitis may indicate a cholesterol saturation no greater than does a ratio of 20 in normal bile.

As a matter of fact, there are still unknown factors which keep cholesterol in solution in bile. The presence of phosphatides and of neutral fats and fatty acids in bile may exert a considerable influence in keeping cholesterol in solution. This is especially true of bile in which the bile acid concentration is very low. In such bile there may be a bile acid-cholesterol ratio as low as 1 (table 9).

The very high total bile acid-cholesterol ratio found in both the gallbladder bile and the hepatic bile of patients with hepatitis and with acute obstruction of the liver supports the conception, suggested by Wright and Whipple,<sup>10a</sup> that the excretion of cholesterol in bile is a

10. (a) Wright, A., and Whipple, G. H.: Bile Cholesterol: Fluctuations Due to Diet Factors, Bile Salt, Liver Injury, and Hemolysis, *J. Exper. Med.* **59**:407, 1934. (b) McMaster, P. D.: Studies on Total Bile, *ibid.* **40**:25, 1924. (c) Dostal, L. E., and Andrews, E.: Etiology of Gall Stones: III. Effect of Diet on the Bile Salt-Cholesterol Ratio, *Arch. Surg.* **26**:258 (Feb.) 1933. (d) Bac-

function of the hepatic parenchyma independent of bile acid excretion. After acute injury to the liver it is evident that the excretion of cholesterol practically ceases while the percentage of bile acids excreted, although reduced, is still considerable. The relatively unchanged concentration of cholesterol in continued hepatic drainage, in spite of fluctuations in bile acid concentration, further supports the conception of a relatively independent cholesterol function of the liver cells. Similarly, the oral administration of bile salts, both to man and to the dog, has little influence on the concentration of cholesterol excreted by the liver, although desoxycholic acid seems to have a slight tendency to increase the cholesterol concentration.

If the excretion of cholesterol is dependent on some function of the liver cells which is reduced by acute injury, may it not be concluded that the rather high excretion of cholesterol in cases of disease of the gallbladder is due to hyperfunction of the hepatic cell? Such speculations raise questions as to the factors which influence the excretion of cholesterol by the liver. Within the limits of the physical factor of solubility, the excretion of bile acid has little influence on the excretion of cholesterol. It is known, however, that cholesterol metabolism is bound up in some way with lipid metabolism. Gallstones are more common in stout persons, who increase their fat depots readily and for whom reduction of weight is very difficult. Excretion of biliary cholesterol is greatest during starvation,<sup>10b, c</sup> when the metabolism of fats is greatly increased. In acute pancreatitis there seems to be a somewhat increased excretion of biliary cholesterol (table 11). Bacmeister<sup>10d</sup> found evidence of increased biliary excretion of cholesterol by persons with diabetes in whom metabolism of fats is encouraged by a high fat diet. However, Dostal and Andrews<sup>10e</sup> were not able to confirm this. Experimental work on both dogs and human beings indicated that the administration of a high fat diet has no influence on the biliary excretion of cholesterol.<sup>10a, c</sup> Our own experiments on a human being (table 15) indicate that a prolonged high intake of fat has a tendency to raise the biliary excretion of cholesterol. It must be remembered that the biliary excretion of cholesterol in man, as compared with that in other species, is exceptionally high. The only other species studied that has a high bile cholesterol concentration is the pig, whose predisposition to deposit fat, if not abnormal, is certainly exceptional.

The points presented here are brought out to emphasize that further investigation should be directed not to the bile acid-cholesterol ratio but to the factors, probably associated with lipid metabolism, which

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meister: Untersuchungen über Cholesteril Ausscheidung in menschlichen Gallen, *Biochem. Ztschr.* **26**:223, 1910. (e) Fox, F. W.: The Composition of Human Bile and Its Bearing upon Sterol Metabolism, *Quart. J. Med.* **21**:107, 1927.

modify the excretion of bile cholesterol. The evidence recently presented by Dragstedt<sup>11</sup> that the pancreas secretes a hormone which is involved in the metabolism of fat is suggestive of a possible mode of attack on the problem.

If cholesterol tends to precipitate in bile in which the bile acid-cholesterol ratio is lowered, our evidence indicates that the ratio may be readily raised by the oral administration of bile salts. It is raised especially after the administration of cholic acid or of ox bile salts, which contain a high percentage of cholic acid. This seems to be due to the fact that in man the administration of cholic acid is more effective than the administration of desoxycholic acid in raising the concentration of bile acids in hepatic bile.<sup>12</sup>

### CONCLUSIONS

The normal total bile acid-cholesterol ratio in human bile as determined in our studies was about 20. In cases of early chronic cholecystitis the ratio averaged 13, while in cases of advanced chronic cholecystitis the ratio averaged 7.7. The danger of the precipitation of cholesterol is only slightly increased, since the relative amount of the most effective solvent, desoxycholic acid, is greatly increased. In cases of acute cholecystitis the average total bile acid-cholesterol ratio was 6. The high cholesterol concentration increases the possibility of precipitation out of solution.

If the liver is injured, as in hepatitis, in inflammation or in acute obstruction, the excretion of cholesterol is much more markedly reduced than is the excretion of bile acids.

Evidence is presented which suggests that the excretion of biliary cholesterol is controlled by some independent function of the hepatic cell, which is related to lipid metabolism.

The bile acid-cholesterol ratio is readily raised by the oral administration of large amounts of bile salts, especially cholate. This may diminish the danger of the precipitation of cholesterol from the bile.

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11. Dragstedt, Z. R.; Van Poohaska, J., and Harms, H. P.: Observations on a Substance in Pancreas (Fat Metabolizing Hormone) Which Permits Survival and Prevents Liver Changes in Depancreatized Dogs, *Am. J. Physiol.* **117**:175, 1936.

12. Doubilet, H.: Hepatic Excretion in Man of the Various Bile Acids Following Their Oral Administrations, *Proc. Soc. Exper. Biol. & Med.* **36**:50, 1937.

# REVIEW OF UROLOGIC SURGERY

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## KIDNEY

*Anomaly.*—Braasch and Merricks<sup>1</sup> reported a series of 27 cases of proved renal agenesis observed at the Mayo Clinic from 1909 to the present time. The diagnosis was established at operation in 14 cases and at necropsy in 13 cases. In another series of 42 cases, the diagnosis was inferred from roentgenographic and cystoscopic data. This makes a total of 69 cases.

The most frequent subjective symptom was pain on the side on which the kidney was present, which occurred in 38 of the 69 cases. The pain was usually dull, although in 8 cases it was rather severe.

Findings at physical examination were normal in 46, or 66 per cent, of the 69 cases. In the 23 cases in which abnormal conditions were observed, the presence of a palpable mass in the flank on the side on which the kidney was present was the most frequent finding; it occurred in 17, or 24 per cent, of the total number of cases. The next most fre-

1. Braasch, W. F., and Merricks, J. W.: Clinical and Radiologic Data Associated with Congenital and Acquired Single Kidney, *Tr. Am. A. Genito-Urin. Surgeons* 30:103-112, 1937.

quent finding was tenderness to palpation on the side on which the kidney was present; this occurred in 11 cases, or 16 per cent.

Cystoscopic observation of the trigon often will reveal signs suggestive of renal agenesis. Hypertrophy of the interureteral ridge on the side on which the kidney is present usually is well defined, and there is complete absence of the ridge on the other side. Compensatory hypertrophy of the ureteral orifice is usually evident, and urinary expulsion at this point is as a rule more energetic and frequent.

The average size of the normal kidney as measured by means of 100 consecutive excretory urograms was 12 by 6 cm. In 24 cases of renal agenesis the average size of the male kidney was 15.7 by 8.1 cm. and that of the female kidney was 14.8 by 7.1 cm. Thus, the long axis of the kidney averaged 0.9 cm. more for men than for women, and the width for men was 1 cm. greater than for women.

Measurements of the acquired solitary kidney were made with roentgenograms taken in 31 cases observed during the last six months. The average renal outline measured 14.7 by 7.1 cm. In the 8 instances in which the patients were women the average size was 14.6 by 6.6 cm. In the 23 instances in which the patients were men the average size was 14.7 by 7.2 cm. Thus, the chief difference was in the width of the renal outline. The degree of hypertrophy of the acquired single kidney is distinctly less than in cases of renal agenesis. These findings negate the opinion held by some surgeons that if a kidney on exploration is found to be normal and not hypertrophied there must be a functioning kidney on the other side.

There is a relative increase in size of the renal pelvis, which does not equal that of the parenchyma. Little difference in the size of the renal pelvis exists in cases of congenital or acquired single kidney. The renal outline generally is situated lower in cases of renal agenesis than in cases of acquired single kidney or normal kidney. This may be regarded as a definite factor in differential diagnosis. The outline of the psoas muscle is less sharply defined on the side on which the kidney is absent in urograms taken in cases of congenital and acquired single kidney than in an unselected series of urograms. In a few cases of agenesis there is an increase in the width of the psoas muscle on the side on which the kidney is absent.

Beer and Ferber<sup>2</sup> reported a series of cases of crossed renal ectopia (unilateral, fused or elongated kidney). Their report is in agreement with others previously published in that the left kidney was crossed more

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2. Beer, E., and Ferber, W. L. F.: Crossed Renal Ectopia (Unilateral, Fused or Elongated Kidney), with Report of Fourteen Cases Clinically Diagnosed and Two Cases Encountered at Autopsy During the Past Eighteen Years, *J. Urol.* 38:541-561 (Dec.) 1937.

often than the right (9 cases as compared with 7). Also, more of the patients were men than were women (12 patients as compared with 4, respectively). They have noted an autopsic incidence considerably higher than is indicated by the reports of others (condition observed twice in a series of 7,400 autopsies). They have observed the presence of a mass in 9 cases, an important factor in directing attention to the possible presence of this condition. Pain was the outstanding symptom, occurring 8 times. In 5 cases there were no symptoms. In 13 cases the correct diagnosis was made by roentgenologic examination after the presence of some anomalous renal condition had been suspected during the course of ventral suspension of the uterus. The condition in 2 cases was discovered at necropsy. They observed 2 cases in which the kidneys were unfused. This is an incidence of 13.5 per cent, which is consistent with Pagel's figure. Their series presented a rather high incidence of pathologic involvement (66.6 per cent). The prime complication was hydronephrosis. Calculus was present in 3 cases. An operative procedure was performed in 3 instances after a correct preoperative diagnosis had been made.

Beer and Ferber<sup>2</sup> concluded that the diagnosis of crossed ectopic kidney never will be missed if opaque ureteral catheters are employed in every instance. In the future this condition unquestionably will be discovered oftener by means of excretory urograms. The presence of a unilateral mass resembling an enlarged kidney in shape should arouse suspicion of the possible existence of crossed renal ectopia. The anomalous position of the pelvis, the ureter and the vessels accounts for the relatively high incidence of obstructive hydronephrosis. When conditions requiring surgical intervention exist within either kidney the necessary procedure can be performed without hesitancy after the true anatomic arrangement has been determined preoperatively.

Mackenzie and Hawthorne<sup>3</sup> stated that the ectopic kidney is one which by reason of its abnormal embryologic development does not occupy the normal renal position. This anomaly is rare in comparison with the frequent condition of acquired renal ptosis, but the two conditions are easily differentiated.

Mackenzie and Hawthorne observed 11 cases of ectopic kidney in 15,000 admissions to their general service; in 6 instances the condition occurred among male patients and in 5 among female patients. Among the men, the ectopic kidneys of 4 were situated on the right side in the lower lumbar region or the upper sacral region. One was on the left side and was pelvic in type, and 1 showed a left crossed ectopy with lateral fusion to the right kidney. All of the 11 patients had symptoms

3. Mackenzie, D. W., and Hawthorne, A. B.: *The Ectopic Kidney*, Tr. Am. A. Genito-Urin. Surgeons 30:121-139, 1937.

referable to the displaced kidney. In 5 cases there were pressure symptoms but infection was not present.

The authors concluded that congenital displacement of the kidney is rare, occurring once in every 1,000 cases, although some types of this anomaly are seen more frequently than others. Infection, hydronephrosis and formation of calculus frequently are associated with this abnormality. Symptoms were present in all of Mackenzie and Hawthorne's cases, although they were not always considered urologic symptoms at the onset. Pelvic ectopia among women frequently occurs during pregnancy, and in such cases it can be dealt with by cesarean section before term. Elevation of the kidney, although at times successful, is usually a failure owing to the shortness of both the ureter and the renal pedicle.

Lower <sup>4</sup> stated that there are two types of cases in which one may be called on to treat the single diseased kidney: (1) cases of congenital absence of one kidney or congenital solitary kidney and (2) cases of acquired single kidney in which nephrectomy has been performed. With the first condition, congenital single kidney, there is no way of anticipating the disease. With the second condition, acquired single kidney, the possibility of subsequent disease may be anticipated by noting at the time of operation the pathologic changes in the kidney that is removed. In a series of 325 cases of nephrectomy the condition most frequently necessitating removal of a kidney was calculous pyonephrosis. Of the patients with this condition, 9.8 per cent had stone in the other kidney at the time of nephrectomy.

Tuberculosis was the condition for which the next largest series of nephrectomies was performed. Of the patients with this type of involvement, 12.36 per cent later had trouble with the remaining kidney, although tuberculosis could not be demonstrated at the time of the operation. The next series comprised cases of hydronephrosis; 10 per cent of the patients had trouble in the remaining kidney.

From the investigation of this series of cases and from his own experience in dealing with the diseased single kidney, Lower concluded that the first step should be one of conservatism. Although there is a large reserve in the kidneys under normal conditions, there is no reason why too much of this reserve should be sacrificed unless it becomes an absolute necessity. He suggested that conservative treatment in some cases would be better than a radical operation, especially when the lesion is likely to be bilateral. When the physician is confronted with a solitary diseased kidney, naturally there is only one procedure, that

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4. Lower, W. E.: *The Problem of the Single Diseased Kidney*. Tr. Am. A. Genito-Urin. Surgeons **30**:113-120. 1937.

is, conservation. When the symptoms are caused by obstruction the kidney must be drained either by ureteral catheterization or by pyelotomy or nephrostomy.

*Calculus.*—After a review of the material in one of the large clinics in Vienna, Bibus<sup>5</sup> came to the conclusion that mechanical factors are largely responsible for the formation of renal stones as well as vesical stones. Disturbance of mobility, that is, formation of residual urine in the upper part of the urinary tract, is the most important factor. He concluded that urinary infections also influence the formation of stones. When stones occur bilaterally, Bibus stated that the surgeon should choose for the first operation neither the kidney which is in better condition nor that which is more diseased, on the basis of these facts alone; the kidney which endangers the life of the patient or which is itself in danger of destruction should be treated first.

Randall, Eiman, and Leberman<sup>6</sup> stated that calcium plaques in the renal papilla were observed at necropsy in 140 of 609 cases, that is, in 22.9 per cent. In the same series of necropsies 49 renal papillae were observed with stone adherent thereto, and in practically every instance the stone was growing from a deposit of calcium in the papillary wall. In 25, or 4.1 per cent, of the 609 cases stone was observed at necropsy. They attempted but failed to reproduce this formation of calcium plaques in lower animals by administration of diets deficient in vitamins.

A staphylococcus toxoid was concentrated by the rabbit's kidney plasma. The administration of a stable streptococcus hemolysin lenkocidin effects highly suggestive results, causing local damage to the epithelium of the collecting tubules. After the administration of parathyroid extract to dogs for six months a calcium plaque was observed in one renal papilla, identical with that which had been seen in man. It was pointed out that the occurrence of renal calculus in man is essentially only a symptom of some underlying pathologic condition of a renal papilla and that its entire development is a slow, chronic process. Acute symptoms produced in the laboratory with experimental subjects are not comparable with the clinical picture.

Papayoannou<sup>7</sup> stated that he has had good results in the removal of giant coralliform stones by dividing his operation into two or even three stages. Stage I consists of exposure of the kidney and complete

5. Bibus, B.: Urolithiasis bilateralis, Ztschr. f. urol. Chir. u. Gynäk. **43**: 293-332 (Aug.) 1937.

6. Randall, A.; Eiman, J. E., and Leberman, P. R.: Studies on the Pathology of the Renal Papilla: Relationship to Renal Calculus, J. A. M. A. **109**:1698-1702 (Nov. 20) 1937.

7. Papayoannou, T.: La lithonéphrotomie en deux ou plusieurs temps, J. d'urolog. **44**:242-249 (Sept.) 1937.



exteriorization of its convex external border, compresses being placed about it to keep open the surgical incision of the walls. Stage 2 consists of nephrotomy performed by thermocautery, to drain out the pus and remove the calculi if they are mobile. If, however, they are ramified and coralliform and are adherent to the renal parenchyma, their removal is postponed and is performed as a third stage, twenty-four or forty-eight hours later.

Lithonephrotomy in two or three stages is indicated principally in cases of unilateral or bilateral calculosis in which infection is severe, renal function deficient and medical treatment inefficacious. In such a case the patient becomes worse from day to day, possibly owing to pyonephrosis, uremia or glycosuria or to a poor cardiac condition. Unless an emergency arises the patient first should be put in the best possible condition; his resistance should be built up so that he can bear the operation satisfactorily, without suffering from shock. All the usual examinations and tests are carried out. Vaccination, especially auto-vaccination, prior to operation is an excellent measure to prevent septicemic complications. He should be fortified by injections of serum containing dextrose; the myocardium and the digestive system must be cared for meticulously as an indispensable part of the preparation. The least negligence in carrying out these details may cause disaster.

An illustrative case is reported in which the good results are attributed to performance of the operation in three stages, preceded by the building up of the patient's powers of resistance. The author stated that if he had used this technic in one of his early cases, to which he referred, operative shock and death of the patient would not have occurred. Experience in the treatment of 10 patients since that time, on all of whom he performed the operation in two or three stages, led him to report the details of his successful management.

One hundred and seventy-seven patients who had nephrolithiasis but who were not operated on at the time the diagnosis was established were observed by Priestley and Braasch<sup>8</sup> for an average of eleven years to determine their subsequent clinical course.

It was noted that: (1) Eighty-one and eight-tenths per cent of all unilateral stones and 97.8 per cent of all bilateral stones that were not removed surgically caused further symptoms referable to the urinary tract; (2) "silent" stones caused subsequent symptoms less frequently (66.66 per cent) than did stones which previously had caused pain (96.6 per cent); (3) large stones caused subsequent symptoms and necessitated later operation more frequently than did small stones; (4) stones in a calix caused subsequent trouble less often than did stones

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8. Priestley, J. T., and Braasch, W. F.: Late Results in the Conservative Management of Nephrolithiasis, *J. A. M. A.* **109**:1703-1705 (Nov. 20) 1937.

in the pelvis; this was especially true of stones in the tip of a calix; (5) a kidney which contained a stone but which was normal on pyelographic examination caused serious symptoms less frequently than did a kidney which was definitely abnormal on pyelographic examination; (6) impairment of renal function increased the likelihood of serious symptoms and the necessity for subsequent operation, and (7) the presence of gross infection in association with stone definitely increased the incidence of subsequent symptoms referable to the kidney.

*Tumor.*—Patch<sup>9</sup> reported 3 cases of renal tumor. The first was carcinoma of a crossed heterolateral ectopic kidney without fusion. The patient, a man aged 51, had the symptoms of slight enlargement of the prostate gland and slight transient hematuria for one year. He had noticed fulness in the lower part of the abdomen during this time. Examination gave evidence of moderate enlargement of the prostate gland; a mass was present in the right lower quadrant of the abdomen, extending upward to a point just below the level of the umbilicus. Retrograde pyelographic examination gave evidence of slight dilatation of the pelvis of the right kidney. The left catheter crossed the midline and extended upward to the level of the second sacral segment. The left kidney was not injected. The preoperative diagnosis was tumor in a crossed heterolateral ectopic kidney without fusion. This diagnosis was confirmed at operation. The tumor was a large clear-celled carcinoma of the hypernephroid type.

Patch discussed the nomenclature and the reported cases of crossed renal ectopic kidney, both fused and nonfused, and concluded that there has not been a previous report of a tumor associated with crossed heterolateral ectopia without fusion.

Borchardt described an adenoma weighing 12 pounds (5,443 Gm.), which occurred in what he considered a congenitally crossed ectopic kidney, but Patch<sup>9</sup> said that it undoubtedly was an acquired crossed variety, the ectopia being the result of displacement by the enormous tumor. Six other cases have been reported of acquired crossed ectopia from displacement by a large tumor or cyst.

In the second case a malignant leiomyoma occurred in a man, aged 55, who gave the clinical history and had the symptoms and signs of a right renal tumor. The mass was removed; it contained an infiltrating tumor almost entirely replacing the right kidney and invading the renal vein. Sections proved it to be leiomyoma which in some places had undergone sclerosis and in others showed sarcomatous change.

Small leiomyomas frequently are found at necropsy; such tumors, however, have little clinical significance. Patch's case makes the eighth

9. Patch, F. S.: Three Unusual Primary Kidney Tumours, *Brit. J. Urol.* 9:339-358 (Dec.) 1937.

case of large renal tumor reported. Six of the tumors occurred in women and 2 in men. Four of the tumors were malignant.

The third unusual primary tumor of the kidney was a malignant transitional cell papilloma with local metastasis, arising in a loculus of an old hydronephrotic atrophic region in which there had been obstruction at the ureteropelvic junction owing to kinking, bands and adhesions. A malignant papilloma filled several of the loculi of the sac.

Hydronephrosis from obstruction of the renal pelvis by papillary tumors is frequent. No similar case of malignant papilloma arising in a loculus of an old hydronephrotic sac has been reported.

Bailey and Harrison<sup>10</sup> reported 5 cases of large benign renal neoplasm, discussing the pathologic picture and clinical behavior of the lesions. They stated that the problem of operative removal of large benign renal tumors is chiefly a question of correct approach. In 4 cases in this series, in which the tumor was removed by operation, the procedure was carried out by transperitoneal approach. In 1, removal was attempted through a lumbar incision but the renal pedicle was difficult to secure. The procedure was abandoned, therefore, and the tumor later was removed transperitoneally. The vascularity of the tumor, so strikingly demonstrated by the distended venous channels on its surface, is no longer a problem once the renal pedicle has been ligated.

Large dilated blood vessels on the surface of the tumor were present in all the cases. Bailey and Harrison emphasized this fact on account of the frequent presence of the same condition in association with malignant tumor of the kidney. Such a condition does not necessarily signify that the tumor has extended into the renal vein. It is reasonable to assume that the mere bulk of the new growth may so compress the renal vein as to cause dilatation of its collateral vessels. After the operation all 4 patients did well, and none of them had any recurrence of tumor.

The 4 patients were part (5.8 per cent) of a series of 68 patients on whom nephrectomy was performed for tumor. In view of the infrequency with which hypernephroma reaches such a size before operation is performed, the proportion of benign lesions among large renal neoplasms is even greater. Bailey and Harrison concluded, therefore, that patients who have large tumors and who give no evidence of metastasis always should be subjected to operative exploration.

Alcorn<sup>11</sup> reported a case in which a Wilms tumor occurred in an adult. He stated that Kilbane and Lester in 1929 found only 15 such

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10. Bailey, O. T., and Harrison, J. H.: Large Benign Renal Neoplasms: Their Pathology and Clinical Behavior, with Report of Five Cases, *J. Urol.* **38**: 509-529 (Dec.) 1937.

11. Alcorn, K. A.: Wilms' Tumor in an Adult: Report of a Case, *Proc. Staff Meet., Mayo Clin.* **12**:692-694 (Nov. 3) 1937.

cases described in the literature. Since then several additional cases have been recorded.

The patient described by Alcorn<sup>11</sup> was a man aged 45, who noticed a swelling in the region of the left kidney for six weeks. During this time he noticed aching pain in this region and lost about 35 pounds (15.9 Kg.). Hematuria had not occurred. Physical examination revealed an emaciated man with a large fixed mass about the size of a grapefruit in the left renal region. An intravenous urogram showed no evidence of function on the left side. There was no clinical or roentgenographic evidence of metastasis. The right kidney appeared normal. Nephrectomy was performed on the left side, and the pathologist reported a Wilms tumor weighing 1,310 Gm., which had destroyed 90 per cent of the renal substance. The immediate postoperative convalescence was entirely satisfactory. A course of five roentgen treatments was given soon after the operation and was repeated one month later, at which time a general examination of the patient showed essentially normal conditions and a gain in weight. Three months later the patient was reexamined. At this time he was emaciated, and there was a large, firm mass in the lower half of the abdomen. There were many obvious regions of metastasis present. Inasmuch as a correct preoperative diagnosis of Wilms tumor was not established, a preliminary course of roentgen therapy was not given prior to operation.

Of 95 patients who had renal carcinoma and whose cases were reported by Fetter,<sup>12</sup> 58 (61 per cent) were subjected to operation, and 17 (29.82 per cent) of these were living after periods ranging from five months to thirteen years and three months; 36 (63.15 per cent) at the time of the follow-up had died, including 6 (5.2 per cent) who died after the operation.

Renal neoplasms are considered renal carcinoma because true columnar epithelial cells forming definite acini and papillae may be demonstrated. The term hypernephroma is used only to refer to tumors of adrenal tissue.

The surgical approach to the kidney should depend on conditions in the given case and on the surgeon's judgment. With the aid of preoperative irradiation many renal tumors decrease in size; the lumbar route, therefore, may be employed more frequently in the future than it has been in the past.

Fetter<sup>12</sup> concluded that preoperative irradiation is a definite aid to surgical intervention in the practical management of such neoplasms. He concluded also that routine postoperative irradiation has extended the period of survival of many patients.

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12. Fetter, T. R.: Renal Carcinoma: A Study of Ninety-Five Cases, with Follow-Up Notes on Thirty-Six, *J. A. M. A.* **110**:190-196 (Jan. 15) 1938.

Higgins<sup>13</sup> reported the cases of 5 patients who had squamous cell carcinoma of the renal pelvis, seen at the Cleveland Clinic. Including the records of their cases, the literature now contains 64 reports of squamous cell carcinoma of the renal pelvis.

The relation between leukoplakia and squamous cell carcinoma of the renal pelvis frequently is cited in the literature. The striking relation between renal calculi and squamous cell carcinoma has been noted by many observers. It has been stated by some authors that the development of such metaplastic changes may be induced by long-continued irritation due to chronic inflammation of renal calculi. This seems especially probable, because a review of a number of reports of cases indicates that the presence of chronic inflammation of the renal pelvis or calculi seems definitely to antedate the presence of the malignant lesion.

No symptoms are definitely pathognomonic of squamous cell carcinoma of the renal pelvis. Each of Higgins' patients complained of symptoms referable to pyuria due either to a calculus or to chronic inflammation. They also complained of pain in the back. The latter symptom has been present in 43 per cent of cases in the collected series. Loss of weight is a late manifestation, usually occurring after metastasis has taken place.

Two types of lesions predominate: In the first type the cells early invade the renal parenchyma and eventually replace it. The second type of lesion is confined chiefly to the renal pelvis; the region is covered with tumor which in some areas has a papillary appearance. With this type, involvement of the ureteropelvic junction occurs earlier, and a severe degree of hydronephrosis, with atrophy of the renal parenchyma, is found.

Early diagnosis followed by nephrectomy is the procedure of choice. In Higgins' series, in which high voltage roentgen therapy was employed preoperatively, there was no evidence of reduction in the size of the tumor. Postoperative roentgen therapy is advisable.

The prognosis is grave because of the frequency of metastasis. In a review of the literature, Higgins was unable to find the report of a patient who was free from metastasis at the end of five years.

Patch<sup>14</sup> reported 9 cases of tumor of the pelvis and ureter. Six of the tumors were in the pelvis, 2 being benign papilloma, 1 malignant papilloma, 2 squamous cell carcinoma (in 1 case associated with leukoplakia) and 1 transitional cell carcinoma.

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13. Higgins, C. C.: Squamous Cell Carcinoma of the Kidney Pelvis, *Tr. Am. A. Genito-Urin. Surgeons* 30:13-33, 1937.

14. Patch, F. S., in discussion on Caulk, J. R.: Tumors of the Renal Pelvis and Ureter, *Tr. Am. A. Genito-Urin. Surgeons* 30:71-73, 1937.

Patch recalled the tendency of papilloma of the pelvis to recur farther down in the urinary tract. In addition to complete ureterectomy performed at the time of nephrectomy, careful observation of the bladder during a long postoperative period is advisable.

Patch pointed out also that the picture in cases of pelvic and ureteral tumor, particularly of the latter, is likely to be dominated by hydronephrosis; careful urographic examination is particularly important in such cases.

Wolff and Donat<sup>15</sup> cited the report of Lindau, who in 1926 described the anatomic picture of a dysontogenetic disease which he called "angiomatosis of the central nervous system." The principal changes are the formation of hemangioma in different parts of the brain, the medulla, the spinal cord and the retina, associated with malformations in other organs, that is the liver, the pancreas and the kidneys. The complex malformations of the kidney have never been described. Wolff and Donat examined a man aged 37 who had Lindau's disease; cystic hypernephroid changes had occurred in both kidneys. They gave a detailed description of the anatomic changes in this case, with photographs. The portion destroyed both kidneys very little normal parenchyma. There remained in was replaced by tumor containing a mixture of cysts and hypernephroma. Twelve such cases have been described in the literature.

Ordinary cysts of the kidneys are frequently associated with hemangioma of the central nervous system. Adenoma and fibroma are rarer. In two thirds of all cases of Lindau's disease there is evidence of malformation of the kidneys, possibly originating in the development of the organ. The coincidence of malformation of the kidneys and lesions of the central nervous system characterizes two other diseases: tuberous sclerosis of the brain and the dysencephalia splanchnocystica of Leiden.

*Hydronephrosis.*—Walters, Cabot and Priestley<sup>16</sup> stated that plastic operations on the renal pelvis are indicated (1) if hydronephrosis producing symptoms is present on both sides; (2) if hydronephrosis is present in a solitary kidney, and (3) if there is hydronephrosis of one kidney in the presence of a damaged or abnormal kidney on the other side.

Since 1929 various types of plastic operation have been carried out in 71 cases at the Mayo Clinic up to January 1937. In this group there was a mortality during hospitalization of 2.81 per cent.

15. Wolff, K., and Donat, R.: Die Nierenveränderungen bei der Lindauschen Krankheit an Hand einer Beobachtung von cystisch-hypernephroider Umwandlung beider Nieren, *Ztschr. f. urol. Chir. u. Gynäk.* **43**:272-292 (Aug. 12) 1937.

16. Walters, W.; Cabot, H., and Priestley, J. T.: Operative Results in Noncalculus Hydronephrosis: Results in Seventy-One Plastic Operations, *J. Urol.* **38**:688-693 (Dec.) 1937.

Conclusions were based on a study of 46 of the 71 cases, 25 being excluded for the following reasons: In 8 cases there was not satisfactory evidence in regard to the conditions at reasonable periods after the operation; 2 patients died, and in 15 cases nephrectomy was done.

The types of operation were as follows: (1) resection of the renal pelvis (21 cases); (2) resection with reimplantation of the ureter (9 cases); (3) reimplantation of the ureter (3 cases); (4) division of one or more abnormal vessels to the lower pole (2 cases); (5) ureterolysis (2 cases); (6) ureteropyeloneostomy (4 cases); (7) miscellaneous procedures (5 cases), and (8) nephropexy combined with various of the procedures mentioned (19 cases).

Nephrostomy alone was employed in 5 cases. Nephrostomy as an adjunct to various plastic operations was employed in 48 cases.

Secondary nephrectomy was required in 15 cases, or 21.12 per cent. It does not appear that these unfavorable results were associated with any particular type of operation. Thus, in 9 of the cases resection was performed, whereas in each of the remaining 6 cases a different type of operation was done. It will be noted that 12 of the 15 patients were treated by nephrectomy within the first year; 1 two and a half years later, and 2, seven years later.

With the exclusion of certain cases for various reasons, Walters, Cabot and Priestley<sup>16</sup> had 46 cases on which to base their report on operative results in cases of hydronephrosis; reports were made on the basis of pyelographic evidence (26 cases) and also on the basis of reports by letter (20 cases). They have not considered as conclusive any pyelographic evidence which was obtained less than seven months after operation. The group of cases in which reported results were based on pyelographic evidence includes, therefore, cases in which pyelographic studies were done from seven months to more than seven years after the operation.

Considering first all of the various types of operations together, they have classified on pyelographic evidence the results in 5 cases as excellent and in 8 as good; in 5 others the condition of the patients was classified as improved, and in 8 others as not improved. Of the remaining cases, classified on the evidence of letters, in 7 the results have been classified as good; in 8 others the condition of the patients was classified as improved, and in 5 others as not improved. The total results, from evidence both of the pyelogram and of the letters, are as follows: in 5 cases, excellent; in 15, good; in 13, condition improved; and in 13, condition not improved. In a word, 33 of the 46 patients (71.7 per cent) have benefited definitely by the operation, and 13 have not.

Judged by the aforementioned criteria, the results for patients for whom the operation was classified as "resection of the renal pelvis" (21 patients) indicate that of 9 for whom the reported results were based

on pyelographic evidence, the condition of 4 was classified as excellent; that of 1, as good; that of 1, as improved; and that of 3, as not improved. Classified as to results reported on the basis of letters, among 12 patients, the condition of 4 was classified as good; that of 5, as improved, and that of 3, as not improved.

In the cases in which the operation was classified as "resection of the renal pelvis with reimplantation of the ureter" (9 cases), the results based on pyelographic evidence indicate that the condition of 3 patients was classified as good and that of 1 as improved; in cases in which results were reported on the basis of letters, the condition of 2 patients was classified as good; that of 1, as improved; and that of 2 as not improved.

With the help of Rein's thermostromuhr Maatz and Krüger<sup>17</sup> examined the different reactions of the blood stream of the kidney in experimental hydronephrosis in dogs. A rise in the blood pressure of the renal pelvis calls for a decline in the blood supply of the kidney. This decline is the same in the arteries and in the veins. It is proportional to the height of the pressure in the renal pelvis, but is much lower than was anticipated from the results of earlier anatomic investigations. The explanation of this is an active dilation of the blood vessels. The intraparenchymal rise in fluid content which is observed in the renal tissue as early as two hours after ligature of the ureter does not cause a diminution in the flow of the blood stream. The blood supply of a fully developed hydronephrotic kidney is less than 25 per cent inferior to the blood supply of the opposite healthy kidney with its compensatory hypertrophy. In cases of closed hydronephrosis of three weeks' duration even the most vigorous stimulation of diuresis causes only a slight rise of pressure in the renal pelvis; hence a serious mechanical disturbance of circulation of the blood in this state is improbable. The inhibition of the renal blood supply does not seem to be of such importance as a cause of atrophy of renal parenchyma in cases of hydronephrosis as is accepted at present.

Lubash and Madrid<sup>18</sup> attempted a modification of the original Küster operation, ureteropyeloneostomy for hydronephrosis. The ureter is removed from its original site as near its insertion in the pelvis as possible, as the strictured region is utilized in its reimplantation. From this point on, the method as originally given by Küster is carried out for the most part. There is a difference, however, in the method of anastomosis. The ureter is incised downward on its anterior and pos-

17. Maatz, R., and Krüger, E.: Das Verhalten der Nierendurchblutung in der experimentellen Hydronephrose, *Ztschr. f. Urol.* **31**:756-770 (Nov.) 1937.

18. Lubash, S., and Madrid, A.: Uretero-Pyeloneostomy for Hydronephrosis, with Case and Experimental Reports, *J. Urol.* **38**:634-642 (Dec.) 1937.



terior surfaces for a distance of 2 or 2.5 cm., and after its insertion into its new mouth at the most dependent portion of the renal pelvis the straps of the ureter are drawn outward laterally from the pelvis through two small stab wounds on either side of the new neostomy, and a mattress suture is employed to fix them in position. The knots are placed outside the renal pelvis. From this point on, Papin's method of transrenal drainage and resection of the redundant pelvis is carried out. Both the Garoeau catheter that serves as a splint for the new anastomosis and the Pezzet catheter that drains the kidney are brought out through the same nephrostomy wound. Nephropexy is employed if the kidney has been mobilized.

Work on 4 experimental subjects with this method has proved gratifying. The experimental stage has been divided into two separate periods, the work during first period being limited to the ligation of the ureter and the formation of hydronephrosis. The ligature about the ureter was tied 2.5 cm. from its renal insertion, by means of silk threads.

A period of two to five months was allowed to elapse before the second stage (plastic repair) was performed. All experimental subjects survived. The tests for renal function, as performed by the insertion of the Pezzet catheter, showed return of function in a very short time after plastic repair.

Hepler<sup>19</sup> stated that from the etiologic standpoint dilatation of the upper part of the urinary tract, occurring in children, may be divided into three types: (1) that due to mechanical obstruction, most frequently to congenital fibrosis, muscular hypertrophy or exaggerated constriction at the points of normal anatomic narrowing, that is, the ureteropelvic and ureterovesical junctions and the vesical outlet; (2) that occurring as a sequela of a neural condition, either central or peripheral, involving the bladder (such as poliomyelitis, cerebrospinal syphilis, spina bifida, toxic neuritis or the less definite dysfunctions classified as idiopathic); and (3) that for which no obvious cause, either mechanical or dynamic, can be demonstrated.

Hepler<sup>19</sup> discussed functional imbalances at the ureterovesical junction as a possible cause in some cases of dilatation of the third type.

The lower and intramural part of the ureter and the vesical trigon may be considered an anatomic and physiologic unit. These structures have a common embryologic origin which is distinct from that of the rest of the bladder. The muscles of the trigon are formed from a continuation of the longitudinal fibers of the ureters, the lateral extensions forming Bell's muscle and the mesial extensions, which unite with

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19. Hepler, A. B.: Nonobstructive Dilatations of Upper Urinary Tract in Children. *J. A. M. A.* **109**:1602-1606 (Nov. 13) 1937.

those of the opposite side, forming Mercier's bar. Fibers from the central muscle of the trigon loop about the intramural portion of the ureter.

Pharmacologically it has been shown that this unit has a common nerve supply and responds to drugs differently from the rest of the bladder. It receives fibers from the hypogastric nerves only and stimulation of these nerves produces strong contraction of the intravesical portion of the ureter, where the ganglions are most numerous, and of the adjacent trigon.

This neuromuscular arrangement has considerable functional significance; although there is no circular muscle comparable to the anal sphincter, it acts in a similar manner and takes a part in ureteral dynamics. There is active relaxation with opening of the orifice synchronous with the termination of the peristaltic wave. This is followed by a period of contraction, or expulsive effort, at which time the orifice is of pinpoint size and is drawn upward and outward with the adjacent trigon or ureteral mound. There may then be partial relaxation followed by a second contraction, or expulsive effort, after which there is complete relaxation and the slitlike orifice returns to its normal position and shape. The process is comparable to the action of the levator ani muscles in completing the act of defecation.

There may be disturbances in ureteral activity which are comparable to those recognized in like mechanisms for the emptying of a tube of involuntary or smooth muscle with a sphincter at its distal end, such as the gastrointestinal tract. Two types of functional imbalance at the ureterovesical junction are recognized: (1) increased tonicity, or spasm, and (2) absence of the usual active relaxation synchronous with the termination of ureteral peristalsis, or achalasia. The resistance to ureteral emptying caused by these dysfunctions sets in motion the same physical and dynamic factors which produce dilatation in cases of mechanical obstruction. Compensation is more likely to occur in cases of functional imbalance than in cases of mechanical obstruction, because resistance to ureteral emptying is likely to be less unyielding; hence the observation of ureterectasis out of proportion to pelvic dilatation and the absence of elongation and tortuosity.

In some cases congenital idiopathic dilatation considered as a primary embryologic developmental defect may in fact be secondary to a segmental imbalance or to abnormal activity of the sphincter. Hepler<sup>19</sup> discussed 4 cases in which nonobstructive dilatation was observed among children; the condition was assumed to be caused by achalasia at the ureterovesical junction. Hepler also gave criteria for the recognition of this condition.

The association of megaloureter and megalocolon in the case of a child was of interest in view of the contention that the pathogenic

mechanisms of the two conditions are similar. The indications for treatment of a condition which is so little understood and concerning which there have been so few clinical data are not clearly defined. The following methods have been advocated: (1) presacral neurectomy; (2) plastic resection of the ureterovesical junction; (3) incision of the junction by high frequency current, and (4) gradual dilation for high degrees of obstruction.

Foley<sup>20</sup> described a new plastic operation for stricture at the ureteropelvic junction. A large incision which provides adequate exposure and complete freeing of the kidney is essential. By careful examination the exact anatomic relations responsible for obstruction are determined. Adhesions between the pelvis and the ureter are severed completely, which accurately exposes the ureteropelvic junction. The latter is examined carefully by inspection, by palpation and, if necessary, by instrumental exploration through a small pyelotomy. By these means the presence or absence of "stricture" is determined and the question of the need for plastic operation is answered.

The kidney and ureter are held in position to give facility in accurately placing the Y incision in the pelvis and ureter. The stem of the Y is placed in the lateral wall of the ureter and thus will face the pelvis when normal position is restored. The incision is carried through the ureteropelvic junction and downward in the medial wall of the pelvis for an appropriate distance below the ureteropelvic junction. From this point the incision continues as two diverging limbs in the lower medial wall of the pelvis, in the form of an inverted V. The incision in the ureter should equal in length the incision in the pelvis plus the length of the V-shaped flap. The triangular opening in the pelvis and the triangular flap of pelvic wall when turned down face directly the incision in the ureter.

The apex of the flap approximates directly the lower angle of the ureteral incision. By closely spaced interrupted sutures of 0000 chromic catgut embracing only the muscularis (with careful avoidance of the mucosa) the edges of the ureteral incision and the edges of the triangular defect in the pelvis are approximated directly, the tip of the flap fitting neatly into the lower end of the ureteral incision.

When the suturing is completed a soft rubber catheter of size 10 or 12 French is introduced through a small stab opening on the posterior surface of the pelvis and is directed into the ureter for a distance of 6 or 8 cm. A number of small fenestrations are cut in the portion of catheter that is to lie within the pelvis. The catheter serves as a splint for the sutured segment and provides for drainage of urine from the

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20. Foley, F. E. B.: A New Plastic Operation for Stricture at the Uretero-Pelvic Junction: Report of Twenty Operations, *J. Urol.* **38**:643-672 (Dec.) 1937.

pelvis. It is left in place for about a week. A second catheter, extending only into the pelvis, is introduced for use in through and through irrigation.

The operation described has been employed 20 times, in 19 different cases; this is one of the largest series of plastic operations for hydronephrosis to be reported.

In practically all cases reexamination by pyeloureterographic study, functional tests and reports as to relief of symptoms were obtained at long intervals after the operation. In almost half the cases the time from the date of operation to the preparation of the report was seven years or more and 15 of the 19 patients were living at the time of the report. Symptomatic relief was obtained in all cases, and in all but 3 cases the report was obtained a year or more after the operation. In 6 cases it was obtained seven years or more after the operation. In all but 1 case (in which death occurred postoperatively) functional tests and reexaminations according to the methods mentioned were made to determine the condition after operation.

Quinby<sup>21</sup> stated that the treatment of hydronephrosis depends for its success first and most appreciably on the absence of infection both at the time of operation and after operation. This factor is of such importance that every effort should be made to sterilize the kidney by the administration of urinary antiseptics both by mouth and by local application before any plastic procedure is undertaken. Preliminary nephrostomy with antiseptic lavage throughout the drainage tube may be a wise first step for obstinate hydronephrosis accompanied by infection. It has been Quinby's experience that the promotion of better drainage of the kidney by a plastic operation will not in itself be sufficient to allay the infection. Even if the plastic operation is followed by adequate healing the infection will persist, and it will eventually destroy the kidney.

There are two main types of hydronephrosis: (1) that due to anomalous development of the kidney and its appendages and (2) that secondary to the formation of stones or to obstruction in the urinary tract. Hydronephrosis of the first type due to arterial anomaly or, more rarely, to venous anomaly is treated with outstanding success by some form of plastic correction of the underlying anomaly. Other, more gross anatomic anomalies offer still further problems, for example, renal fusion or ectopia. Cases of hydronephrosis of the second type offer, on the whole, much less hopeful prospect of cure by a plastic operation, for the lesion often is bilateral and when first seen is accompanied in many instances by severe infection. In this group, correction of the hydronephrosis itself frequently is of secondary importance to relief of the

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21. Quinby, W. C.: Factors Influencing the Operative Procedure in Hydro-nephrosis, *J. Urol.* **38**:673-679 (Dec.) 1937.

underlying pathologic condition. If this can be accomplished, the hydronephrotic kidney will be found in many instances to retain a respectable amount of function and will cause no symptoms, although its pelvis may seem grossly abnormal on pyelographic examination. Unconquerable infection, however, will spoil all surgical efforts. Nephrectomy, when possible, is then the only relief.

Kafka<sup>22</sup> reported the case of a girl aged 4 months who had congenital hydronephrosis on the left side. The condition was so advanced that the kidney was a unilocular cyst with a thin wall of renal parenchyma. Hydronephrosis resulted from atresia of the ureter, which began at the pelvis and extended downward, making a diverticular pouch about 1 cm. in length. Nephrectomy was performed, and the child recovered. At the same time there was congenital dislocation of the right hip, for which operation was performed a year later. Six years later the child was in excellent condition.

Crabtree<sup>23</sup> stated that pregnancy does not alter the position of the kidneys. If the renal shadow gives evidence of an abnormal relation to other organs, the condition is generally due to anomalies antedating pregnancy. Abnormalities of the calices, pelvis and the ureter may be attributable to pregnancy, but rounded calices have not the same significance when they occur in pregnant women as when they occur in patients who are not pregnant. Congenital abnormalities of the pelvis and ureter and preexisting alterations caused by disease generally are recognizable in cases of pelvic dilatation due to pregnancy, as pregnancy may exaggerate previously existing conditions.

When intravenous pyelographic examination shows the lower two thirds of the ureter completely filled, the condition should be considered pathologic. There is sufficient evidence to reestablish the fact that relaxation of the muscles of the renal tree associated with pregnancy may be due to the effects of pregnancy on the endocrine glands.

The excretion of drugs used for intravenous pyelographic examination is apparently retarded by pregnancy both of women and of experimental animals. Decreased motility in cases of large pelvic and ureteral dilatations interferes with diffusion of the excreted dye and thus produces a less satisfactory demonstration of the pelvis and ureter.

The essential differences between a chronic obstructive lesion and an obstructive lesion which has its origin in pregnancy must be recognized. The former is characterized by hypertrophy of the muscles, decompensation after the limit of hypertrophy has been reached and changes due to fixation, which limit indefinite dilatation.

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22. Kafka, V., Jr.: Ein Fall von Hydronephrose bei einem 4 Monate alten Säugling bei gleichzeitigem Bestehen einer Hüftgelenksluxation, *Ztschr. f. Urol.* **31**:602-606 (Sept.) 1937.

23. Crabtree, E. G.: Hydronephrosis of Pregnancy, *J. Urol.* **38**:605-619 (Dec.) 1937.

The abnormalities in the pelvis and ureter which are attributable to pregnancy are distinguished by the absence of hypertrophy, probably a result of endocrine influence. Surgical treatment in the latter cases has a more favorable prognosis.

A number of occurrences of hydronephrosis cannot be explained by intrinsic obstructions, and it becomes necessary to search carefully for extrinsic causes. It must not be forgotten that extrinsic and intrinsic causes may coexist. Long-continued pressure on the ureter from the outside often produces damage within the ureter, resulting in inflammatory changes, fibrosis and obstruction, which may remain after the extrinsic cause is removed, thereby seriously impairing the symptomatic and pyelographic result. Bobbitt<sup>24</sup> divided these extrinsic causes into four groups: (1) aberrant polar vessels and fibrous bands, (2) renal, abdominal or retroperitoneal tumor, (3) trauma with defective innervation and (4) fibrosis of the ureter, due to irradiation or to involvement of the ureter by a malignant growth.

Ekehorn was probably the first to direct attention to the part played by aberrant polar vessels in the causation of hydronephrosis. By reason of the fact that aberrant vessels frequently lie close to the ureter there has been considerable opposition to his work. Bobbitt concluded that increased mobility of the kidney or inflammatory changes in the region of the ureteropelvic junction, or both, usually is the inciting factor in this type of obstruction. He has found fibrous bands or adhesions in a rather small percentage of cases.

Large abdominal tumors certainly must be listed as occasional causes of hydronephrosis, although in Bobbitt's experience they are seen rarely, owing probably to the fact that in these days of modern surgical treatment for such tumors operation is performed early and often the condition is so apparent that no pyelographic study is made.

Traumatic injuries to the kidney and the surrounding structures can cause hydronephrosis in different ways. Braasch explained that also play an important role in hydronephrosis. Neuromuscular conditions there is a group of cases in which pyelectasis occurs with no apparent cause for ureteral obstruction. He has noted a hypertonic condition of the muscles which produces contractions at the ureteropelvic junction so violent as to cause protrusion into the lumen, producing a true ball valve action.

In reviewing the intrinsic causes of hydronephrosis, Mathé<sup>25</sup> divided them into three categories: (1) congenital, (2) acquired and (3) traumatic.

24. Bobbitt, R. M.: Extrinsic Causes of Hydronephrosis, *J. Urol.* **38**:562-573 (Dec.) 1937.

25. Mathé, C. P.: Intrinsic Causes of Hydronephrosis, *J. Urol.* **38**:574-592 (Dec.) 1937.

Congenital hydronephrosis unassociated with other anomalies of the urinary apparatus exists as a distinct clinical entity and is probably far more frequent than is conceded in the literature. Associated stones are caused by pre-existing stasis; accessory vessels and ptosis play a minor role and are factors only in the late stages of the development of hydronephrosis. Valve formation or high insertion of the ureter is a result of pelvic dilatation rather than its cause. Hydronephrosis frequently accompanies a malformation of the kidney or ureter, such as bifid and double pelvis and ureter, fused, ectopic and horseshoe kidney, aberrant distribution of blood vessels or congenital structure and valve formation of the ureteropelvic junction. With such conditions hydronephrosis may accompany the renal anomaly at birth; or poor drainage resulting from malformation may produce hydronephrosis later in life, superimposed infection playing an important role.

Acquired hydronephrosis resulting from mechanical obstruction at the ureteropelvic junction or the upper part of the ureter long has been recognized. In a great number of cases of hydronephrosis the condition is so caused. Of interest is the dynamic type of hydronephrosis due to neuromuscular dysfunction either associated or not associated with pyelonephritis.

Traumatic hydronephrosis is a clinical entity. It is usually the result of late sequelae of, and is occasionally the immediate result of, direct or indirect trauma to the kidney. Obstruction is produced by strangulation of the ureter due to cicatricial changes resulting from organization following extravasation of blood and urine in the perinephrium. In rare instances hydronephrosis is due to obstruction from blood clots, sudden displacement of the kidney or dislodgment of pre-existing renal calculi.

*Tuberculosis.*—Mathé<sup>26</sup> has observed 6 cases of unilateral renal tuberculosis in which the condition occurred in children and adolescents aged 2, 10, 13, 16, 17 and 18 years, respectively. Four patients are living and in good health ten, eight, three and two years after operation, respectively. Two died six months and five years, respectively, after operation as the result of generalized spread of the disease.

In reviewing 4,698 cases of unilateral renal tuberculosis, Mathé found that this disease was present in 565 patients (12 per cent) between the ages of 1 and 20 years; there were 20 occurrences (0.42 per cent) in children from 1 to 5 years of age; 51 occurrences (1.08 per cent) in children from 5 to 10 years of age, and 494 occurrences (10.5 per cent) in adolescents between 10 and 20 years of age. The statistics

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26. Mathé, C. P.: La tuberculose rénales de l'enfant, Arch. d. mal. d. reins 10:517-544 (Nov.) 1936.

of autopsies show that the disease is much more frequent at the latter age (25 to 30 per cent more frequent).

Despite the perfection of cystoscopes of small caliber and despite the increased use of roentgenographic tests for renal function, many pediatricians and physicians do not always take advantage of these methods of research when they examine children suffering from chronic infection of the urinary tract.

Although autonephrectomy and quiescence of symptoms have been regarded as indications of spontaneous cure of renal tuberculosis, the treatment best suited to the unilateral type among children as well as among adults is nephrectomy, and if this operation is carried out sufficiently early it results in a large proportion of cures. It is probable that in cases of renal tuberculosis of the unilateral surgical type, in which the condition later may become bilateral, cure of the disease in the kidney is not effected. According to the reports, tuberculous kidneys that have undergone calcification, with total occlusion of the ureter and with cessation of symptoms, amount to about 0.5 per cent. Spontaneous cure probably never occurs. For this reason early nephrectomy is the procedure of choice and is the only means of relief for the children who compose the other 99.5 per cent of patients.

*Pyelonephritis.*—Wharton, Gray, and Guild<sup>27</sup> stated that only 2 of 30 girls and young women who had pyelitis in infancy and childhood and who were examined (on the average) nine and six-tenths years after the last attack of pyelitis were found to be in poor health. Only 1 had been treated for any urologic disease since the occurrence of pyelitis in childhood. This young woman had been an invalid owing to chronic urinary infection. She had lost one kidney, and the remaining kidney was hydronephrotic and infected.

Twenty-eight had had average good health since childhood; most were in excellent health. The vast majority had no complaints; symptoms, when present, could be elicited only by questioning. Follow-up urologic examinations showed that 17 (57 per cent) had definite abnormalities in the urinary tract at the time of reexamination. Of 9 who had had only one attack of urinary infection in childhood, 6 showed urinary abnormalities. Of 21 who had had recurring infections in childhood, 11 had urinary abnormalities at the time of reexamination.

General results of the reexamination showed that 10 had mechanical abnormalities demonstrable by intravenous urographic study. Ten had varying numbers of leukocytes in the catheterized urine. In 15 cases cultures of the urine yielded bacteria. Two patients had small stones.

27. Wharton, L. R.; Gray, L. A., and Guild, H. G.: The Late Effects of Acute Pyelitis in Girls, *J. A. M. A.* 109:1597-1602 (Nov. 13) 1937.



One girl, aged 15 years, had a functionless kidney with practically no symptoms. Three young women had borne children; 1 had pyelitis while pregnant.

In a series of 200 cases of chronic pyelonephritis recently observed at the Mayo Clinic by Braasch,<sup>28</sup> bacilli of the colon group were found in 110 cases. *Escherichia coli* was present in 84 cases, or 42 per cent, and *Aerobacter aerogenes* in 26 cases, or 13 per cent.

Next in frequency, cocci are found in the urine in cases of chronic pyelonephritis. In the series of 200 cases they were found in 28, or 14 per cent. Their presence is noted often on microscopic examination of the urinary sediment when cultures are sterile. Some bacteriologists regard them not as etiologic factors but as unimportant secondary invaders and as being frequently the result of contamination.

Streptococci are found only occasionally in the voided urine in cases of chronic pyelonephritis and less frequently when the urine is catheterized. In the series of 200 cases of pyelonephritis they were present in only 8 cases, or 4 per cent.

*Proteus* was found to be the infecting organism in only 6 cases, or 3 per cent. This organism is not satisfied with being an indolent invader causing chronic infection; either it exercises its destructive activities so as to destroy the kidney with diffuse purulent infection or malignant formation of stones, or it disappears after a short period of infection.

In the series, bacterial pyuria was found in 44 instances, or 22 per cent. It was observed most frequently in cases of advanced renal infection of long standing accompanied by cicatricial changes or by impaired renal function.

A review of the 200 cases showed that the  $p_H$  of the urine, with but few exceptions, fell in the neutral zone, between 5.9 and 6.5.

A complication which frequently is observed in association with chronic renal infection is that of secondary formation of stone. In a series of 526 cases of chronic bilateral pyelonephritis observed at the clinic in the past seven years, secondary lithiasis was found in 28. Lithiasis secondary to chronic pyelonephritis is often bilateral, as is shown by the fact that stones were found in both kidneys in 9 cases of this group of 28, or 32 per cent. When bilateral the stones usually are multiple. Unilateral stones were found in 19 cases; they were single in all but 4. When there is chronic bilateral pyelonephritis and a stone is present in one kidney the renal infection usually is primary, because infection which occurs secondary to stone seldom is transmitted to the other kidney.

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28. Braasch, W. F.: Clinical Data Concerning Chronic Pyelonephritis, *J. Urol.* 39:1-25 (Jan.) 1938.

Renal hematuria is not an infrequent complication; it occurred in 67 of 526 cases. It can be distinguished from other forms of renal hematuria because it is usually accompanied by evidence of infection, as a rule involving both kidneys.

In considering the treatment of chronic pyelonephritis, it is interesting to compare the remedies of yesterday with those employed today. Lavage of the renal pelvis and the bladder, formerly employed as a matter of routine, has been largely superseded by other therapeutic measures. Although eradication of infection is not to be expected by means of lavage, this measure is still indicated in cases of excessive pyuria and in the treatment of secondary hematuria.

Vaccines, which formerly were employed in spite of unconvincing results, are now largely discredited.

Reference frequently has been made to the possibility that foci of infection, such as occur about the teeth and also in the tonsils, the prostate gland and the uterine cervix, are sources of renal infection. Although such foci are often of clinical importance in the causation of acute or recurrent renal infection, they are not so important in the causation of chronic pyelonephritis. Removal of these foci does not usually have much effect on the course of chronic renal infection; the time for their removal is long past, because the infection has become so thoroughly intrenched in the renal tissues that removal of the original source no longer has much therapeutic value.

The presence of infection in the prostate gland and the seminal vesicles may be the cause of persisting renal infection; such infection apparently may act not as a distant focus but as a direct source of ascending infection. Efforts to eradicate renal infection are often futile because of subsequent reinfection from these persistent foci. Buchtel has shown that sulfanilamide is present in the prostatic secretion in sufficient concentration to be bacteriostatic. He stated that it is of material aid to massage in reducing prostatic infection. Although removal of infected teeth and tonsils has not directly benefited patients with chronic renal infection in many cases, experience has shown that it can materially affect the progress of infection of the prostate gland, and eradication of these foci should be insisted on.

Deformity (demonstrable by urogram) which accompanies chronic pyelonephritis and which is regarded as characteristic consists of caliectasis and ureterectasis with cicatricial narrowing of the infundibula and the renal pelvis. The dilatation of both the ureter and the calices usually is adynamic. On the other hand, pyelectasis, which is comparatively infrequent, is likely to be the result of obstruction. Dilatation of the ureter is usually of greater diagnostic importance than is dilata-

tion of the calices. Adynamic or atonic ureterectasis may be explained by periureteritis affecting the trophic nerves which supply the ureteral wall.

Surgical treatment, the need for which is surprisingly infrequent in these cases, usually is not indicated unless one of the following conditions is present: some form of obstruction; localized, persistent infection; destruction of renal function; or atrophy. Such treatment was found necessary in only 3 per cent of the 526 cases of chronic pyelonephritis observed by Braasch<sup>28</sup> at the Mayo Clinic in the past seven years.

In the recent developments of chemotherapy, compounds have been produced which have given startling results: sulfanilamide and mandelic acid. Although sulfanilamide gives promise of being a potent factor in eradicating renal infection in many cases, in common with other similar drugs it is of greater value against acute than against chronic infection. There is a vast difference in the results obtained in treatment of chronic and of recent renal infection. Although most renal infections when acute, subacute or recurrent can be controlled by recently developed chemotherapy, the secondary and anatomic changes associated with chronic infection often will defy all treatment.

Eradication of chronic pyelonephritis is possible by prophylaxis and by thorough, intelligent treatment of acute and subacute infection. Treatment of urinary infection still demands the intelligent supervision of the urologist.

In 2 cases in which the patients were men reported by Albright, Dienes and Sulkowitch,<sup>29</sup> roentgenograms of the kidneys showed multiple deposits of calcium in the pyramids. The deposits were larger and of less uniform size than those seen in cases of nephrocalcinosis associated with hyperparathyroidism. Small gram-negative bacilli were present in the urine of both patients; the organism was identified as *Haemophilus influenzae*. The urine of both patients was constantly alkaline, probably owing to the property of *H. influenzae* to split ammonia from urea, and the deposits of calcium were presumably attributable to the alkalinity so produced. Sulfanilamide promptly eliminated *H. influenzae* from the urine, with resulting acidity of the urine.

*Parenchymal Infection.*—Hamer<sup>30</sup> stated that metastatic renal infection includes a group of lesions of the kidney, due to blood-borne infection, with which there is no urogenital abnormality acting as an accessory cause. The source of the infection is usually some remote peripheral focus, such as a carbuncle, a boil, an infected wound or an

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29. Albright, F.; Dienes, L., and Sulkowitch, H. W.: Pyelonephritis with Nephrocalcinosis Caused by *Haemophilus Influenzae* and Alleviated by Sulfanilamide: Report of Two Cases, *J. A. M. A.* **110**:357-360 (Jan. 29) 1938.

30. Hamer, H. G.: Diagnosis and Treatment of Metastatic Renal Infection, *J. Urol.* **38**:530-540 (Dec.) 1937.

infection of the respiratory tract. The organism is usually a pyogenic coccus. The lesion is a miliary abscess, massive abscess, carbuncle, perinephritis or perinephric abscess. The clinical picture includes pain in the region of the affected kidney, costovertebral tenderness and fever of the septic type. The laboratory findings indicate that the urine is essentially normal; staphylococci may be produced in smears or cultures, and a large number of leukocytes may be present in the blood. Roentgenologic examination may give evidence of clouding of the renal region, obscuration of the shadow of the psoas muscle and scoliosis. Pyelograms may show compression, filling defects and inflammatory fixation of the kidney. Incision and drainage will effect a cure in the majority of cases. In a few the condition requires nephrectomy.

*Embolism.*—Westerborn<sup>31</sup> reported the case of a man aged 49 who had recurrent emboli from chronic endocarditis. The first embolus went to the brain, causing temporary paralysis of the left side of the body. Six months later an embolus lodged in the right femoral artery. This was removed, and the patient recovered. In the next four months he had two more emboli, to the mesenteric arteries and to the brain. He recovered completely. Two weeks later an embolus blocked the right renal artery. During attempted removal the thrombus slipped from the artery to the kidney and was crushed by hand as well as possible. After this maneuver the circulation in the kidney and the renal function were reestablished temporarily. Five weeks later this kidney was functionless, and nephrectomy was done. The kidney was atrophied to one-third its size at the first operation. Eight months later an embolus lodged in the left renal artery, with complete block. Eighteen hours later embolectomy was performed, but the circulation was never reestablished, and the patient died of uremia. This was probably the first time that operative removal of an embolus from the renal artery was attempted.

Westerborn<sup>31</sup> attempted to determine how long the renal artery could remain obstructed and resume its function after the reestablishment of circulation. He ligated the renal artery in each of a series of rabbits, observing the renal function later by excretory urographic examination. He also examined the removed kidneys after the death of the animal. When the artery was kept ligated less than eighty minutes the kidney retained its function and its anatomic structure was unchanged. When anemia was of longer duration the function was maintained only in exceptional cases. He found that with the rabbits

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31. Westerborn, A.: *Embolie in der Arteria renalis mit Bericht über einen operierten Fall, sowie über experimentelle Untersuchungen darüber, wie lange die Blutzufuhr nach der Niere abgesperrt sein kann, ohne dass ihre Funktionsfähigkeit aufgehoben wird*, Ztschr. f. Urol. 31:687-708 (Sept.) 1937.

in which circulation to the kidney was obstructed for over ninety minutes the kidney was destroyed completely.

Westerborn concluded that the same conditions prevail in man and that it may be possible to preserve a human kidney obstructed by embolus, but only if the embolus can be removed within possibly the first hour after obstruction. This time might be extended if the obstruction is not complete. The obstruction probably was not complete in Westerborn's case, in which the crushing of the embolus forty-eight hours after obstruction reestablished temporary renal function.

*Pelvic Pain.*—The renal pelvis varies so markedly within normal limits that it is difficult to set any normal standards. Notwithstanding this fact, Minder<sup>32</sup> concluded that there is a definite connection between infection, pain and the form of the pelvis. The fact that a renal pelvis is anatomically normal is not proof that its function will be normal. A disturbance of urinary excretion may cause the same amount and type of trouble as are caused by morphologic changes of the renal pelvis. The position of the kidney is of little importance in relation to the situation of pain. Abnormality of the ureteropelvic junction together with infection increases the incidence of pain in the case of any diseased kidney. A low or ptotic kidney should not by itself cause pain.

*Renocolic Fistula.*—Wesson<sup>33</sup> stated that renocolic fistulas occur secondary to a chronic suppurative renal lesion associated with perinephritis or perinephric abscess. He reported cases; the fourth patient, aged 87, died before any diagnostic procedures could be carried out. In 1 case the fistula passed directly from the bowel through the substance of the kidney to a calix. In the other 2 the opening was in the pelvis and was connected indirectly, through a perinephric abscess, with the bowel. In 1 case the fistula developed nine years before the operation, and the patient's good health during the interim was attributed to the treatment of a nonexistent cancer by means of roentgen therapy. A silent renal staghorn calculus was present in 1 case, but the fistula was caused by a proteus infection.

The morbidity and mortality rate from proteus infection in the genitourinary tract is very high.

*Observations on the Capsule.*—Rolnick<sup>34</sup> stated that the true capsule acts as a protective barrier to trauma and prevents the spread of infection to the kidney. There is a constant interchange of fluid on the renal surface, which may be of considerable clinical and physiologic

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32. Minder, J.: Ueber den Zusammenhang zwischen Nierenschmerz, Beckenform und Infektion, *Ztschr. f. Urol.* **31**:586-595 (Sept.) 1937.

33. Wesson, M. B.: Renocolic Fistulae: Reports of Three Cases, *Tr. Am. A. Genito-Urin. Surgeons* **30**:159-167, 1937.

34. Rolnick, H. C.: Some Observations on the Renal Capsule, *J. Urol.* **38**: 421-426 (Nov.) 1937.

importance. This fluid lubricates the renal surface and allows for the constant finding of a plane of cleavage between the capsule and the kidney. Decapsulation is harmful to the kidney. The new capsule consists of scar tissue only; it does not protect the kidney and may interfere with renal function.

*Surgical Technic.*—De Vincentiis<sup>35</sup> stated that there is a wide difference of opinion as to the relative advantages of the electric cutting current and those of the scalpel, some writers regarding the cutting current as indispensable in the surgical armamentarium and others considering its use dangerous to any kind of tissue. He decided to carry out research in a series of operations (nephrotomy) in which the cutting current should be particularly advantageous. De Vincentiis performed histologic and functional studies with a series of 36 rabbits, comparing the value of these two methods of cutting.

After use of the cutting current the concentration of urea in the blood rose even more than when the scalpel was used; it remained at the new level for twelve days. In both cases there was increased elimination of urea in the urine.

With reference to histologic studies, wide nephrotomy performed with the scalpel always is attended by hemorrhage, and despite two transcapsular sutures and compression of the renal pedicle 3 rabbits died of hemorrhage on the second day. When the cutting current was used, no incident of this kind occurred. Although macroscopically there was this marked difference in the incidence of hemorrhage, microscopically the hemorrhagic zone, with reference to extension, did not seem to differ in the two types of intervention. The time required for absorption of the blood was sixteen days after the use of the scalpel and twenty-four days after the use of the cutting current.

In addition, the incision with the cutting current is less sharply defined; the margins of the wound are altered and necrotic, and cicatrization is slower. With the scalpel this process was complete on the sixteenth day; with the cutting current it was not complete until thirty days later.

The consideration that merits most attention, however, is the constant and repeated observation with all the histologic sections that in tissues incised with the cutting current there was extensive necrosis of the parenchyma of the kidney whereas in tissues incised with the scalpel there was little necrosis, and that was limited to the region of the incision. In tissues incised with the cutting current this necrosis was

35. de Vincentiis, A.: Nefrotomia col bisturi elettrico e col bisturi commune (ricerche istologiche e funzionali), Arch. ital. di urol. 14:386-408 (July) 1937.

always wide in extent and was diffused beyond the region of the incision. Moreover, the degenerative processes within the cortex were much more advanced than in tissues incised with the scalpel and consisted of changes which involved indifferently the tubules and the glomeruli. Thus, de Vincentiis concluded that the kidney is extremely sensitive to the electric current. After twenty-four days, and still more completely after one month, the degenerative processes and the zones of necrosis had disappeared from kidneys treated with the scalpel, whereas in kidneys treated with the cutting current degeneration and necrosis were still present, although in less degree, throughout the duration of the observations, which was two months.

Wenzl<sup>36</sup> discussed partial resection of the kidney, which he adopted in 5 cases, with good results in 4. In the other, death occurred from septicemia.

When the kidney is irritated by inflammation and suppuration, the muscular power of the pelvis and ureter is small. It rises spontaneously if the inflammatory foci are eliminated by partial resection or by continuously repeated irrigation through a double-ended nephrostomy tube. A further rise in the muscular power of the uropoietic system can be effected by forcing fluids and by intestinal irrigations with the "enterocleaner." Irrigation acts not only by increasing the amount of fluids excreted through the kidney but by stimulating peristalsis of the excretory urinary system as well. By vigorous contractions the secreted urine is eliminated quickly without leaving residual urine; this hinders the recurrence of urinary calculi.

For prevention of recurrence of formation of stones, the following principles should be observed:

1. Renal stones should be removed before serious infections and degeneration of the kidney have occurred.
2. During operation the pelvis of the kidney should be palpated carefully, and all fragments of stone should be removed.
3. If any infection is present, permanent drainage should be established.
4. In postoperative care, antiseptic washing or treatment with bacteriophage is to be used daily.

#### URETER

*Anatomy.*—Gayet<sup>37</sup> stated that although in certain cases the intramural portion of the ureter presents the classic appearance of an ampulla

36. Wenzl, O.: Ueber die Teilresektion der Niere mit Vorschlägen zur Verhinderung des Nierensteinrezidivs, *Ztschr. f. urol. Chir. u. Gynäk.* **43**:452-475 (Nov. 15) 1937.

37. Gayet, R.: L'uretère intra-mural: Étude anatomo-physiologique. Troubles fonctionnels et leur traitement, *J. d'urol.* **44**:193-217 (Sept.) 1937.

between two contractions, one at the entrance into the bladder wall and the other at the ostium, there is in reality no true ampulla but rather a zone peculiarly dilatable on account of the multiple folds presented by the mucosa. This is proved by the difficulty encountered in injecting the ampulla with an opaque substance in the living subject as well as in the cadaver.

Ureteral muscular fibers do not end at the wall of the bladder but extend all the way to the valve and come to an end not far from its free border. However, they are slender, and the somewhat transparent valve separating the ureter and the bladder for a few millimeters gives the impression that the two mucosae are almost merged into one. When the valve is short the ureter ends at the point of emergence from the intraparietal tract; but when it is long the dimensions of the ureter are somewhat increased.

The musculature of the intramural portion of the ureter consists of an uninterrupted longitudinal layer following the fibers that come from higher up. This layer becomes individualized, expands and reaches its maximal thickness in the midst of the vesical crossing; then the fibers become thinner and diverge to terminate around the ostium without continuing into the musculature of the bladder, of which they are independent. There is no circular layer suggesting a sphincter. The average circular layer of the pelvic portion ends at the bladder. The few arciform fibers that resemble circular layers are inconstant. The sheath of the ureter represents the continuation of the external longitudinal layer, which, well individualized in its pelvic portion, lies spread out over the external surface of the bladder, without mingling with the vesical fibers and without continuing at the level of the intramural portion.

The relations of the bladder and the ureter are intimate, but there is no true continuity between the two organs. Each retains its individuality, and the ureteral muscular fibers terminate at the level of the ostium.\* Connective tissue separates the two musculatures, and no exchange between them can be observed.

Gayet's data agreed with those of Cordier; both found that in the living subject this portion of the ureter cannot be injected or distended with opaque material if it is in a healthy condition. If it is diseased or atonic or if lesions are present in its wall, injection is possible in much more frequent instances; hence, failure to visualize an opaque substance at its level is in favor of its integrity.

The elasticity of the intramural part of the ureter is less than that of the portion above the wall of the bladder but is of good quality in the submucosa, which displays good distensibility. The capacity for dilatation is likewise less than in the portion above. Its sensitivity, on



the other hand, is much greater than elsewhere, owing to the large number of its nerve plexuses and ganglions. Its excitability is also accordingly great. Its contractility is striking, since even if isolated from the bladder and pelvic ureter it possesses autonomous movements. Tonicity reaches its maximum in this zone, as does also rhythm.

The intramural portion of the ureter plays a dual role: dynamic and tonic. The real obstacle to vesicoureteral reflux is found in the intramural portion of the ureter, and the muscle within, which opposes the reflux, is in reality the muscle of the bladder itself.

To functional disturbances of the musculature of the intramural portion of the ureter this structure reacts with anatomic modifications (hypertrophy) and physiologic modifications (hypertonia, to the point of spasm). The results of the latter are supramural retention, without narrowing of the intravesical ureter, due to simple disequilibrium of the habitual conditions of ureteral dynamism.

Functional troubles due to atony of this zone also occur. They may be congenital or acquired. They result in vesicoureteral reflux due to dilatation of the supra-adjacent urinary passages. Acquired atony may be of inflammatory or of nervous origin. Treatment is medical and surgical. Surgical treatment varies according to the case. Cystostomy will ameliorate the graver symptoms of cystitis. In cases of extreme involvement nephroureterectomy may be required, but only exceptionally.

*Anomaly.*—Lepoutre and Dewailly<sup>38</sup> made a study of extravescical openings of the ureters of women. Such a condition is apparently of more frequent occurrence among women than among men. Disregarding exceptional cases, the ectopic ureter corresponds in about a third of cases to a simple kidney, not double; in the other two-thirds it corresponds to a double kidney one ureter of which opens normally while the other opens into the vulva or the urethra. By Weigert's law, the ectopic ureter, the meatus of which is lower, always corresponds to the uppermost of the two kidneys on the side in question. When such a ureter comes from a simple kidney it is always dilated and its parenchyma is atrophic, a point of great importance from the point of view of treatment, because its function is almost nil. Its lower orifice is narrower than a normal orifice. The ureter is dilated and sinuous as a result of defective evolution and chronic infection.

The cardinal symptom of an abnormal ureteral orifice among women is urinary incontinence, which is present from birth, is continuous and is in no way influenced by the patient's posture. In rare cases, however, this symptom does not exist.

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38. Lepoutre, C., and Dewailly, A.: Les abouchements extra-vésicaux de l'uretère chez la femme, *Arch. d. mal. d. reins* 10:551-562 (Nov.) 1936.

Such an abnormal orifice usually opens into the urethra and the vulva; more rarely, it may open into the vagina, and exceptionally, into the uterus or into Gartner's or Müller's duct.

When such an orifice is discovered the first thing to do is to catheterize it. If this procedure elicits liquid the composition of which resembles that of urine, it is probable that the opening is ureteral. Injections of opaque substance may enable the physician to secure a pyelogram of the abnormal ureter (if the latter is capable of being catheterized). Intravenous pyelographic study is seldom of any value. In the great majority of cases the diminutive kidney corresponding to the ectopic ureter will not eliminate the injected substance, for it is functionless; no urographic means of learning from which kidney the ectopic

The most reliable means of learning from which kidney the ectopic ureter proceeds is the retrograde pyelogram revealing the absence of a superior calix on one side alone. Papin attached great significance to this sign. It is not, however, absolute in its value.

The treatment is partial nephrectomy, the extirpation of the small kidney corresponding to the ectopic ureter. Sometimes this cannot be done, and it is necessary to remove the entire kidney on the affected side provided the opposite kidney has good function.

*Injury.*—The question of transverse suture of the ureter has been the object of experimental and histologic studies repeatedly in the last year. E. Wildbolz and Hryntschak have shown that a cross-cut and resutured ureter is able to function normally and that hydro-nephrosis will not develop above if the suture has been made properly. Rubritius<sup>39</sup> reviewed a case which led him to the same conclusions. A man aged 26 had a pyelotomy performed to remove an almost impermeable stone, and during the second operation an almost impermeable hydronephrosis, and plastic reconstruction of the pelvis was carried out. Only a few interrupted sutures were inserted, and the wound was drained. A catheter was used as a splint, and the urinary stream was not deviated. The result after six months was excellent from both the anatomic and the functional point of view.

*Hernia.*—Dourmashkin<sup>40</sup> stated that hernia of the ureter is rare. Seventy previous cases were reported, and with the exception of those in which the condition was observed at necropsy the hernias in all cases were discovered at operation. Dourmashkin cited the first case

39. Rubritius, H.: Zur Querresektion des Harnleiters, *Ztschr. f. Urol.* **31**: 649-652 (Oct.) 1937.

40. Dourmashkin, R. L.: Scrotal Hernia of Ureter, Associated with a Unilateral Fused Kidney: A Case Report, *J. Urol.* **38**:455-467 (Nov.) 1937.

in which a positive diagnosis was made by retrograde and intravenous pyelographic studies. The condition frequently is associated with vesical hernia. It also is associated in the majority of cases with hernia of preperitoneal fat. The latter may be transilluminated, which may lead to an erroneous diagnosis of a collection of fluid in the scrotal sac.

*Ureteroenterostomy.*—Smith<sup>41</sup> stated that ureteroenterostomy in selected cases is an operation which does not carry a prohibitive risk. It was successful in 12 of the last 16 cases in which the simple unilateral technic was used. Coffey's technic no. 2 has been abandoned because of the greater mortality it entails. Ureteral drainage as proposed by Coffey should be carried out promptly if severe pyelonephritis develops. The right ureter may be implanted into the cecum if the sigmoid is not available.

*Bilharziasis.*—Vermooten<sup>42</sup> discussed bilharziasis of the ureter and reported a series of cases illustrating the stage in the progress of urinary bilharziasis at which the urologist is first consulted. This is, as a rule, eight to ten years after the original infestation; rarely are any ova present in the urine.

The diagnosis can be established only by cystoscopic examination. The cystoscopic picture associated with the various manifestations of bilharziasis is generally known. Attention, however, has not been directed toward the roentgenographic appearance of the ureter, which Vermooten<sup>42</sup> regarded as pathognomonic of the disease in its later stages.

In 1930 Harlow and Afifi drew attention to what they described as "cloudy shadows" and calcified demarcations of the bladder and the lower part of the ureter in cases of long-standing bilharziasis. In 1932 Diamantis reported a series of cases of ureteral and vesical calcification in which the condition was due to *Bilharzia haematobia*. In 1934 Afifi, describing the "roentgenographic manifestations of urinary bilharziasis," again drew attention to the "cloudy shadows" and to the "calcified demarcations" of the bladder and the ureters. Vermooten's experience with the South African type of bilharziasis indicated that the calcified demarcations in the advanced stage of the disease are rather rare, although pathologic changes in the lower part of the ureter associated with normal conditions in the proximal part, as illustrated in the urograms in his reported cases, are seen frequently.

The veins which drain the bladder also drain the pelvic portion of the ureter. From this and from general knowledge of the clinical

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41. Smith, G. G.: Recent Experiences with Uretero-Enterostomy, *Tr. Am. A. Genito-Urin. Surgeons* 30:343-346, 1937.

42. Vermooten, V.: Bilharziasis of the Ureter and Its Pathognomonic Roentgenographic Appearance, *J. Urol.* 38:430-441 (Nov.) 1937.

manifestations of the disease it was assumed that in a very large percentage of instances when the bladder becomes infested with *Bilharzia* the pelvic portion of the ureter becomes infested also.

Experimentally, Vermooten<sup>42</sup> has been able to show that if the ureterovesical valve is incompetent regurgitation of urine up a normal ureter at the time of urination will not dilate the ureter but also definite similar circumstances an infected ureter will dilate and remain dilated.

Vermooten also has shown experimentally that partial ureteral obstruction will cause not only dilatation of the ureter but also definite elongation, which is manifested by tortuosities or kinks of the ureter. This was later shown to be true clinically as well as experimentally. The tortuosities or kinks, strangely enough, always seem to occur in the upper half or the upper two thirds of the ureter. Except in cases of infestation with *Bilharzia* this appears to be uniformly true. Presumably the pelvic portion of the ureter is far more fixed than is the lumbar portion.

In cases of ureteral bilharziasis, the ova as a rule are found most frequently in the pelvic portion of the ureter, so that when obstruction occurs at the ureterovesical valve the infested portion dilates, and with the dilatation there is elongation, which should take the form of tortuosities or kinks. For mechanical reasons, the intramural portion of the ureter cannot dilate. As ova are deposited all through this region, the lumen of the intramural portion of the ureter naturally becomes narrowed. With increasing obstruction the entire upper portion of the urinary tract eventually will become dilated also.

Vermooten concluded that as bilharziasis is the only disease that affects primarily the pelvic portion of the ureter without affecting the proximal portion, except in rare instances, dilatation and tortuosity of the pelvic portion of the ureter associated with normal conditions in the lumbar portion of the ureter, in the pelvis and in the calices is and should be regarded as pathognomonic of infestation with *Bilharzia haematobia*.

*Megaloureter*.—Crabtree<sup>43</sup> stated that a large dilated ureter, termed by Caulk megaloureter, is characterized in its earlier stage by fusiform, atonic distention of the lower third of the ureter with comparatively normal conditions in the renal cortex, the pelvis and the upper portion of the ureter. In the later stages of the condition the process of distention reaches and involves the upper part of the ureter and the pelvis. In the terminal stages, thinning of the cortex and "clubbing" of the calices are characteristic findings. In these stages renal destruction has been accomplished either partially or completely. In cases of

43. Crabtree, E. G.: Plastic Operation for the Relief of Megalo-Ureter, Tr. Am. A. Genito-Urin. Surgeons 30:323-342, 1937.

megaloureter the problem of management of the condition is primarily one of the efferent, rather than the secretory, integrity of the renal unit. For this reason the preservation of the secretory organ by correction of the abnormality of its conductive channels becomes a tempting problem for the urologist. This is especially so because not only is the histologic picture of the renal parenchyma practically unchanged microscopically from the normal, in cases in which no infection is present, but the total amount of renal substance which is found above such megaloureters is often about equal to that of the uninvolved kidney on the opposite side, and its secretive ability remains unimpaired for many years.

Megaloureter may be unilateral but is often bilateral. In 2 of Crabtree's cases it was associated with the lone kidney in patients with congenital absence of the other kidney. Infection was absent in only 3 of the cases which he has observed.

Five causes of megaloureter have been recognized. These are obstructions external to the bladder, ureteral stricture of the ureterovesical region, ureterocele, absence of the ureterovesical valve and neurogenic disturbances of the ureter.

The megaloureter is a changed ureter and is considered the end result of three factors: hypertrophy of the musculature of its walls, decompensation after the peak of hypertrophy has been passed and fixation caused chiefly by fibrosis and hyperplasia of the mucosa.

A survey of the literature indicates that four types of treatment have been employed for megaloureter, in addition to the obvious one of correction of pathologic changes in the urethra and the neck of the bladder. They are ureteral dilation, enlargement of the ureteral orifice by surgical operation, ureteral resection by the method of Hinman and ureteronephrectomy.

Ureteral dilation is adequate to produce great improvement in some cases of less extensively changed ureters. It cannot always be done; it is sometimes impossible either to catheterize the orifice or to produce lasting benefit even if dilation is accomplished, because dilation of some strictures produces only fracture of the walls of the stricture.

Various methods of enlarging the orifice in cases of congenital narrowing of the ureterovesical juncture have been devised. The most widely employed method is section of the orifice through the vesical wall and the nearby ureteral wall, after which the mucous membrane of the ureter is sutured to the mucous membrane of the bladder.

Hinman has contributed toward eliminating longitudinal redundancy of the megaloureter as well as toward correction of the ureterovesical defect but has not considered lateral redundancy. He has freed the ureter from the bladder, after which, either by dilatation of the orifice through the vesical wall for reinsertion of the ureter or by creation of

a new vesical opening, he has drawn the ureter through the vesical wall. The excess length of ureter then has been excised and the stump of the ureter anchored to the bladder. He has also resected at other points in the course of the ureter.

Most observers have agreed that if the disease is unilateral and the condition of the other kidney is normal, ureteronephrectomy is the operation of choice.

Crabtree<sup>43</sup> presented the results of plastic operations on megalo-ureter in which attention was paid to elimination of both longitudinal and lateral redundancy of the ureter in one instance and elimination of lateral redundancy alone in the other. These operations were performed in 2 of the 3 cases of megalo-ureter without infection which he has encountered. In the first case end results have been observed after ten years; in the second, after one year. In the first instance nephrectomy was refused by the patient. In the second case the condition occurred in association with a lone kidney.

In the first case the kidney was extensively diseased prior to operation. The kidney was cleared of its infection spontaneously and at the end of ten years had sufficient function to fill by the intravenous method within the average filling time for the normal kidney.

In the second case the kidney improved in function, lent itself to elimination of infection by autisepsis and showed reduction of the combined ureteral and pelvic capacity to .14 cc.

Vermooten<sup>44</sup> in discussing megalo-ureter stated that Chwalla restudied the embryology and the development of the human cloaca and the urogenital sinus, including the early development of the ureter. He found that there was a complete diaphragm across the lower end of each ureter in embryos of approximately the 10 to 20 mm. stage and occasionally in older ones. The diaphragm was composed of only 2 layers of cells. On the one side these resembled vesical epithelium and on the other ureteral epithelium.

Vermooten has investigated a large series of roentgenograms of dilated ureters of children. In many he saw a definite obstruction or a valvelike formation in the region in which the ureter enters the bladder. Such a band or diaphragm may be seen a little above the ureterovesical orifice. For that reason it is conceivable that surgical dilation of the ureter may not completely destroy or remove the remnants of Chwalla's membrane. This condition, of course, is an expression of the obstruction. Relatively little relief, therefore, will be had from the existence of such conditions as ureterocele, diverticulum and other similar congenital anomalies in the region of the ureterovesical orifice.

44. Vermooten, in discussion on MacKenzie, D. W., and Seng, M. I.: Obliteration of a Ureter in an Anomalous Kidney with Hydronephrosis, *Tr. Am. A. Genito-Urin. Surgeons* 30:347-363, 1937.

## PROSTATE

*Hypertrophy.*—Hinman<sup>45</sup> stated that the operation of perineal prostatectomy for hyperplasia of the prostate gland is safe. The modern method of hemostasis and plastic closure controls hemorrhage and shortens the patient's stay in the hospital by half. The functional results are as good as those achieved by any other method, if not better; and they are of equal permanence. Injury to the rectum with the formation of fecal fistula, the only actual disadvantage, is rare. The majority of such fistulas close spontaneously, and the few which do not can be closed surgically with very little risk.

The greatest advantage of the perineal operation over all others used in the treatment of hyperplasia of the prostate gland lies in the relation of hyperplasia to cancer. Cancer of the prostate gland is frequent, occurring in 14 of every 100 men more than 45 years of age. More than 1 of every 5 men who have prostatism have cancer. More than half the patients who have cancer also have hyperplasia of the prostate. Although the two lesions are distinct, any method of treatment of hyperplasia which neglects the possibility of cancer is not a good method. The perineal route is the only one by which both hyperplasia and cancer can be approached successfully at the same time. It is the only route by which a suspicion of cancer can be confirmed and by which operation best suited to all the conditions found can be carried on satisfactorily. The perineal route is the only approach by which radical removal of cancer of the prostate gland unassociated with hyperplasia can be performed with preservation of normal micturition.

Uhle and Melvin<sup>46</sup> reported a case with two recurrences of benign prostatic hypertrophy or tertiary prostatic hypertrophy.

The incidence of recurrence varies between 1 and 2 per cent. In a recent review of 227 cases of benign prostatic enlargement in which operation was done by either the suprapubic or the perineal route at the hospital of the University of Pennsylvania between the years 1923 and 1932, 3 recurrences (1.3 per cent) were observed, including that in the case reported by Uhle and Melvin.<sup>46</sup>

The surgical pathologic picture of benign prostatic enlargement precludes the removal of the prostate gland at operation. Adenomatous tissue is enucleated. Adenoma, during its period of growth, expands and compresses prostatic tissue into a thin shell resembling a capsule. To distinguish this from the true capsule of the prostate anatomists have called it the surgical or false capsule. With pressure removed, the

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45. Hinman, F.: *The Modern Operation of Plastic Perineal Prostatectomy*, Tr. Am. A. Genito-Urin. Surgeons **30**:265-274, 1937.

46. Uhle, C. A. W., and Melvin, P. D.: *Tertiary Prostatic Hypertrophy: An Unusual Case Report*, J. Urol. **38**:487-493 (Nov.) 1937.

prostatic tissue either remains atrophic or regenerates to resume its normal size. Therefore it seems logical to assume that the same cause which produces the original growth may produce the recurrence. Another factor in recurrence, and one that has received theoretical consideration from various authors, is the failure, at the first operation, to notice small spheroids of adenomatous tissue, or the incomplete removal of such processes. If the blood supply is not injured, these small spheroids are capable of regeneration to such an extent that they may interfere with the dynamics of micturition.

*Brucella Infection.*—Boyd<sup>47</sup> reported the discovery by culture of *Brucella abortus* in the prostate gland of a patient with chronic brucellosis. The diagnosis of brucellosis was not made until the bacteria were found in the prostate gland. The patient had been sick for years with symptoms of varying intensity and was sometimes bedridden. Examinations at some of the best clinics in America and by some of the best internists failed to disclose the cause of the illness. Cultures were made from the prostate gland because of the persistence of small groups of pus cells and small groups of fine gram-negative bacilli in the prostatic secretion.

Boyd concluded that urogenital infections from which *Br. abortus* can be cultured are more frequent than is now suspected. Because the diagnosis of chronic brucellosis is often so difficult, cultures of material from the urogenital organs seem quite worth while when the presence of this condition is suspected. Special technic is required for obtaining growths of *Br. abortus* in culture mediums.

*Echinococcus Cysts.*—Liakhovitzky<sup>48</sup> reported a case of primary hydatid cyst of the prostate gland. This condition is rare. In the Russian literature he has found records of only 7 authentic cases; in an equal number of others there were lesions which proved to be retrovesical cysts. The patient was a man aged 25 who was admitted to the oncologic dispensary for sarcoma of the prostate gland. Examination of smears of the blood revealed 7 per cent eosinophils. The results of the various investigations led to a diagnosis of hydatid cyst of the prostate gland. Operation was performed. There are five ways in which such a cyst may be approached: (1) by the extraperitoneal route, through the abdominal integuments; (2) by the perineal section; (3) by incision of the abdominal integuments combined with perineal section; (4) by the transvesical route, and (5) by the transrectal route.

47. Boyd, M. L.: Human Prostatic Infection with *Brucella Abortus* (*Alcaligenes Abortus*). Tr. Am. A. Genito-Urin. Surgeons 30:259-264, 1937.

48. Liakhovitzky, M.: Kyste hydatique de la prostate, J. d'urolog. 44:398-402 (Nov.) 1937.



The first of these was chosen. The tumor was smooth and as large as two fists. After puncture, which elicited a clear fluid, the anterior wall of the tumor was sutured to the edge of the cutaneous wound. When the cyst was opened a large amount of yellow-amber fluid escaped. The chitinous tunic was extracted in a single piece. The cyst was cleansed and drained, and a tampon was inserted. During the first month thereafter, the cavity secreted 10 to 14 cc. of fluid. Secondary hydatids were observed on several occasions and were evacuated. After eight months in the hospital the patient was discharged, at which time he had a small fistula which closed one month later. He was in good general condition and complained only of a diminution in sexual potency.

In most cases reported the clinical picture was that of compression of the urethra as well as of the rectum, the latter symptom predominating. In this case, as in others, the patient had suffered from pain in the anal region and from dysuria and pollakiuria. Except during defecation and urination, the pain had not been acute; the discomfort was more like a sense of heaviness from the pressure of a weight.

The cystoscopic picture is characteristic, showing the rounded form of the grayish red or grayish blue cyst. A transparency is seen near the free border of the tumor, and blood vessels traverse the cystic surface. In the eight operations that have been done in Russia, the transvesical route was used six times; the perineal, once, and the extra-peritoneal through the abdominal wall, once. As to the mode by which the scolices penetrate the prostate gland to produce primary hydatid cyst, the possibility of their arrival through the blood stream must be excluded entirely; so the only possible way is by direct penetration of the rectal wall.

#### BLADDER

*Tumor.*—Higgins<sup>49</sup> stated that cystectomy and transplantation of the ureters had been performed in 34 of his cases of carcinoma of the bladder. A reduction in the mortality was obtained by performing the operation before dilatation of the ureters, renal infection and impairment of renal function had occurred. Less radical operative procedures should be employed in cases of advanced carcinoma of the bladder associated with dilatation of the ureters, pyelonephritis and impaired renal function. Such vesical carcinomas lie beyond the range of operability with this type of surgical procedure.

Patients who survive the operation (and the percentage of such patients is gradually increasing) have satisfactory control of the urine; they may return to their social and business activities in comfort.

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49. Higgins, C. C.: Cystectomy and Transplantation of the Ureters into the Bowel for Carcinoma of the Bladder, *Surg., Gynec. & Obst.* **66**:549-556 (Feb. 15) 1938.

Insufficient time had elapsed to warrant statements as to the percentage of five year cures. The immediate results, however, were gratifying, and Higgins concluded that the outlook is optimistic.

Graves and Dresser<sup>50</sup> have studied the routine records of 24 patients with cancer of the bladder who were given external irradiation as the first direct treatment of their disease.

The average age of these patients was 67.6 years. Nine of them were more than 70 years of age. Most of the tumors were moderately advanced or were extensive. Fifteen were classified clinically as operable; 9 were called inoperable. Most of the tumors involved the region of the trigon of the bladder or were in close proximity thereto. In 12 cases the lesions were recorded as multiple.

Even with a relatively low dosage and with no great emphasis on the method, high voltage roentgen therapy is said to have resulted, temporarily at least, in arrest of hematuria in more than half of our cases. There was gross evidence of some degree of regression, great or slight, in at least half the cases; there was no such evidence in 6 cases, and of 4 cases no record was kept. There was an occasional instance in which it was felt that the amount of regression was sufficient to classify the patient more definitely with the group whose tumors were considered operable.

Some form of operation was deemed necessary, and was employed in 17 cases at varying intervals after high voltage roentgen therapy. The procedures were as follows: suprapubic cystotomy, electrocoagulation and implantation of radium, 10 cases; cystoscopic fulguration and implantation of radon seeds, 4 cases; resection of the anterosuperior portion of the bladder, 1 case; total cystectomy, 1 case, and suprapubic cystotomy, electrocoagulation and packing of the bladder for the emergency control of hemorrhage, 1 case.

Graves and Dresser<sup>50</sup> were aware of no increased technical difficulty at the time of operation because of the previous administration of external irradiation but it was their distinct impression that wounds healed more slowly and were more involved in infection and that the convalescence of the patients was longer and more difficult than in cases in which high voltage roentgen therapy had not been employed as a preoperative measure.

In conclusion, as a result of their study, Graves and Dresser<sup>50</sup> stated that external irradiation with 200 kilovolt equipment by ordinary methods and with ordinary dosage has no place as a curative agent in the routine treatment of malignant tumors of the urinary bladder. As a

50. Graves, R. C., and Dresser, R.: Experiences with High Voltage Roentgen Therapy in the Treatment of Malignant Tumors of the Urinary Bladder. *Tr. Am. A. Genito-Urin. Surgeons* 30:201-207, 1937.

palliative agent it is useful, especially in the arrest of hemorrhage, and in an occasional case sufficient regression may be accomplished thereby to render an extensive lesion more amenable to cure by other means.

Tumors which are amenable to cure by operation or by operative treatment combined with interstitial radiation are still best treated by these means. Apart from its important role as a palliative agent in cases of inoperable tumor, the greatest promise for the usefulness of high voltage roentgen therapy lies in the treatment of radiosensitive types of multiple papillomatosis of the bladder and in the treatment of those conditions, also radiosensitive, in which the tumor has involved both ureters or the region of the vesical neck.

Barringer<sup>51</sup> in a report on radium therapy in 215 cases of carcinoma of the bladder stated that his three year cures were obtained by use of radium in 69 cases, or 32 per cent. Five year cures occurred in 52 cases, or 24.1 per cent (a drop of 7.6 per cent). The total number of cases in which the bladder became free of cancer was 96, or 44.6 per cent. Treatment in these cases was by cystoscope and by suprapubic implantation. They include all cases in which the bladder was opened, no matter how extensive the disease. In many cases of extensive carcinoma, radium was implanted with the idea of controlling metastasis. Notwithstanding this, five year cures fail in about three fourths of all cases.

The factors influencing physicians' choice of therapy are the size, grade and position of the tumor and the condition of the kidneys. Small tumors, papillary or infiltrating, are best treated cystoscopically, either by implantation of radon seeds or by applications of radon. Large tumors, if papillary, are treated by suprapubic implantation of radon. Large tumors, if infiltrating, are treated by methods to be outlined. Tumors of lower grades of malignancy are treated as has been outlined. Tumors of higher grades of malignancy, particularly those of grade 4, are treated if possible by external irradiation and cystoscopically. When a tumor is on the base of the bladder (as are 75 per cent of all vesical tumors), encroaching on the ureters or internal urethra, irradiation therapy is superior to operative removal.

If the kidneys are infected and the ureters and renal pelvis dilated, cystoscopic treatment by radium is superior to the open operation. The suprapubic operation and the massive implantation of radon seeds add to the infection. The implantation or application of radium cystoscopically can be performed in divided treatments.

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51. Barringer, B. S.: Radium Therapy of Bladder Carcinoma: Five-Year Results; Failures; Future Therapy, *Tr. Am. A. Genito-Urin. Surgeons* **30**:209-214, 1937.

One of the disadvantages of radium treatment is that the implantation of seeds into an infected tumor increases the amount of infection present. A slough always is formed, and this presents a focus of increased infection. The slough may become incrustated with calcareous deposits, and stones may form as a result. Asepsis and a certain amount of antisepsis help to obviate this condition. Cleansing of the bladder with antiseptic washes before and after cystoscopic implantation, extreme care in the suprapubic approach and painting of the tumor with mild solutions of iodine before implantation of radium are all helpful.

Vesicovaginal fistulas occur as the result either of implantation of radon or of the depth of the tumor, or both. Barringer<sup>51</sup> had 3 cases of such fistulas. Not only the size of the tumor but the degree of infection and the condition of the kidneys should determine whether the method of treatment is to be suprapubic or cystoscopic. Barringer concluded that the cystoscopic treatment is preferable. If the tumor is ulcerated and infected and if one or both of the kidneys are hydro-nephrotic, suprapubic implantation of a large amount of radon is a dangerous procedure from the standpoint of infection.

The forms of radiation in use include radon seeds; roentgen therapy alone or combined with the use of radon seeds; fulguration and roentgen therapy combined; preoperative and postoperative roentgen therapy, and application of radium. Radon seeds have constituted the best medium for both suprapubic and cystoscopic application of radium. Notwithstanding repeated and persistent attempts to control the more intractable types of cancer of the bladder, high voltage roentgen therapy alone has failed signally. The use of roentgen therapy in the cases of mild cancer of the bladder or of papilloma, which could easily be controlled by cystoscopic fulguration or by application of radium, is unjustifiable, according to Barringer. Barringer has attempted in 3 cases of ulcerated extensive infiltrating carcinoma to combine the use of roentgen therapy and the use of radon seeds. The radium was applied either cystoscopically or suprapubically. All 3 patients succumbed. Considerable work has been done lately with the instrument used for transurethral prostatectomy for fulgurating extensive tumors of the bladder; this was followed by the use of roentgen therapy. No extensive series, according to Barringer, have been reported. It seems that fulguration as an adjunct to roentgen therapy is not as effective as radium.

It would seem theoretically that either preoperative or postoperative roentgen radiation might partially devitalize tumor cells so that operative removal would result in a larger number of cures. Barringer concluded that this is more a theoretic than a practical consideration. The

application of a large amount of radium held against a tumor for periods of one hour by means of the cystoscope under direct vision might seem to offer a chance of controlling a large ulcerating cancer of the bladder. These treatments are supplemented by high voltage roentgen therapy. Barringer<sup>51</sup> had several cases in which this method was used and was effective.

Keyes<sup>52</sup> reported a series of 31 cases in which the patients were observed ten to eleven years after suprapubic implantation of radon seeds into epithelial tumors of the bladder too extensive for control by cystoscope.

Prompt control of recurrences prevents increase in malignancy. Ten cases of grade 1 and grade 2 tumors were reported. In half these cases the tumor recurred, and in 2 cases the patients died of the disease. Yet, thanks to routine cystoscopic studies, half of these patients have been free of tumor for a number of years, and in 2 others the condition has been controlled by cystoscopic observation during the ten years in which the tumors have continued to recur. Tumors of grades 3 and 4 show much less tendency to recur; if not palpably infiltrating they may be controlled in the majority of cases. Of 6 patients, 4 were free of tumor when last seen or heard from, a number of years after operation.

Infiltration palpable on preoperative rectal or abdominal examination is a sign that the tumor is incurable. In this series only 1 such tumor was controlled. Three of the patients died of cancer of the prostate gland. Although necropsy was not performed, the cancer in 1 case was believed to be secondary to a tumor of the bladder or of the urethra.

Deming<sup>53</sup> described a new surgical approach for treatment of carcinoma of the neck of the bladder. A patient who had cancer of the vesical neck and was treated with radical perineal excision of the vesical neck, part of the trigon, the prostate gland and seminal vesicles was reported well after a period of six years. Restoration of normal urination was secured. The comfort of the patient after this operation was extraordinary as compared with the discomfort of the long period during which the patient usually suffers from dysuria after treatment with radium. The technic of the operation is not difficult. Total cystectomy with transplantation of the ureters is not necessary for certain types of cancer which develop at the vesical neck. Radical perineal resection of the vesical neck and the prostate gland for cancer of the vesical neck should be employed more often than has been customary.

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52. Keyes, E. L.: Thirty-One Patients with Bladder Tumor Treated Ten Years Ago by Suprapubic Section and Radon Implantation, *Tr. Am. A. Genito-Urin. Surgeons* 30:215-221, 1937.

53. Deming, C. L.: Successful Radical Perineal Resection of Bladder Neck for Carcinoma, *Tr. Am. A. Genito-Urin. Surgeons* 30:227-234, 1937.

Smith<sup>54</sup> in discussing tumors of the bladder stated that the single or perhaps double small pedunculated tumor, whether it is papillary carcinoma of low grade or frank papilloma, can be successfully treated by excision cystoscopically or suprapubically, with the implantation of one, two or three radon seeds beneath the pedicle of the tumor.

When such pedunculated tumors occur in greater numbers than two it is usually necessary to open the bladder suprapubically so that thorough access may be obtained, but the same process can be employed. In treatment of this type of tumor Smith stated that thorough electrocoagulation of the stump is of value.

With the single, infiltrating tumor the situation is a little different. In Smith's experience electrocoagulation, although temporarily successful, has not produced good permanent results with this type of tumor. Either the entire thickness of the vesical wall should be resected, if that is feasible, or radium should be implanted beneath and about the infiltrated portion of the wall of the bladder, well outside the region of palpable induration.

*Dermoid Cyst.*—Shih and Char<sup>55</sup> reported the occurrence of a dermoid cyst which had ruptured into the urinary bladder.

Symptoms of this condition usually make their appearance at some time between puberty and old age and may be in no way distinctive until rupture into the urinary bladder has occurred. The cysts always contain hair, and the passing of hair in the urine, pilimiction, constitutes a major symptom. Calculous incrustations frequently form around hairs as nuclei, and the passing of stones, teeth and sebaceous material has been observed. Rupture always is followed by complicating cystitis.

Excision of the dermoid cyst is the logical procedure. When it is impossible to dissect the cyst from the urinary bladder, it may be necessary to resect a portion of the vesical wall. Postoperative care consists of drainage of the urine by means of an indwelling urethral catheter, which allows the vesical wound to heal without tension.

*Diverticulum.*—In the course of removal of a diverticulum of the bladder after sudden collapse of the patient, Hryntschak<sup>56</sup> merely severed the diverticulum from the bladder and inserted a drain into the diverticulum.

The postoperative course was astonishing. The patient recovered readily; the drain was removed on the thirteenth day, and there were

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54. Smith, G. G., in discussion on Cabot, H., and Pace, J. M.: *Methods of Selecting the Proper Operative Treatment for Cancer of the Bladder*, Tr. Am. A. Genito-Urin. Surgeons 30:235-258, 1937.

55. Shih, H. E., and Char, G. Y.: *Dermoid Cyst Ruptured into Urinary Bladder*, J. Urol. 38:165-172 (Aug.) 1937.

56. Hryntschak, T.: *Zur operativen Behandlung des primären Blasendivertikels*, Ztschr. f. Urol. 31:659-663 (Oct.) 1937.

no further symptoms from the diverticulum. The prostate gland, which was enlarged, was removed two months afterward by transurethral resection. Searching the literature; Hryntschak found that in a few cases the condition had been treated in the same manner and with good results; always, as in his case, the operation had been done as a makeshift procedure.

The excellent result obtained in his case by exclusion and drainage of the diverticulum combined with transurethral resection of the vesical neck convinced him that this is the best method of procedure in similar cases.

*Injury.*—Stevens and Delzell<sup>57</sup> stated that rupture of the bladder is to be distinguished from perforation. The mortality from the former is higher than that from the latter. Twenty-seven cases of all types of vesical injury involving rupture or perforation are reported. Eight of 14 patients who had intraperitoneal injury died, but death occurred in only 2 of 13 patients who had extraperitoneal injury alone.

Roentgenographic methods are theoretically preferable in arriving at a diagnosis, but cystoscopic study has been applied more readily, and it has given a positive diagnosis in nearly 85 per cent of cases. If operation is performed promptly, we doubt whether it adds to the risk. Diagnosis by catheter is notoriously unreliable. The treatment is to operate promptly and to establish efficient drainage of the site of injury and of the bladder. Stevens and Delzell<sup>57</sup> preferred suture of the traumatic opening, but this is not always essential. Exploratory laparotomy is important, especially in the early stages. Transfusion or treatment of shock may be required before operation can be considered.

*Exclusion.*—Henry Wade<sup>58</sup> reviewed his 60 cases of exclusion of the bladder by diversion of the urinary stream, into the colon in 54 cases, to the surface of the skin in 5 and into a fistula in 1. He concluded that the Coffey-Mayo technic or Coffey's technic no. 1 is the best and that technics no. 2 (tube technic) and no. 3 (transfixion suture) are unsound in principle and inferior in many ways to no. 1. Since 1934 he has performed bilateral simultaneous implantation made possible by immediate intravenous infusion of sodium sulfate solution as advocated by I. L. Dick. This promotes renal secretion and prevents anuria. In the 54 cases of transplantation to the bowel, 36 transplantations have been bilateral and simultaneous, without the use of catheters. Ten additional transplantations have been done for patients who had single kidneys.

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57. Stevens, A. R., and Delzell, W. R.: Traumatic Injuries of the Bladder, with Report of Twenty-Seven Patients Operated Upon, *Tr. Am. A. Genito-Urin. Surgeons* **30**:185-196, 1937.

58. Wade, H.: Vesical Exclusion, *Proc. Roy. Soc. Med.* **31**:277-292 (Jan.) 1938.

Indications for this operation, according to Wade, are congenital malformations, such as complete exstrophy and subsymphysial exstrophy or epispadias among women, vesicovaginal fistula, vesical carcinoma, carcinoma of the cervix uteri treated with radium and followed by vesicovaginal fistula, tuberculous cystitis, interstitial cystitis, urethral stricture with urethral and vesical fistulas and spina bifida with vesical incontinence. Careful preoperative study and preparation are important. Examination by excretory urographic study is essential. The bowel is prepared carefully, and the preliminary use of scopolamine and morphine together with spinal anesthesia provides good relaxation and contraction of the colon. Clamps are not used, and Wade did not approve of any cleansing or packing of the bowel.

The mortality rate in cases of carcinoma of the bladder in which this operation is used is high (51 per cent in Wade's hands, as compared with 25 per cent for nonmalignant conditions). Since January 1936, in a total of 25 cases the mortality has been reduced to 43 per cent for carcinoma and to 9 per cent for nonmalignant conditions. If operation is survived, the danger of ascending renal infection and suppurative pyelonephritis is slight, and with nonmalignant conditions the expectancy of life for the patient is reduced little if at all. A normal, useful and contented life is made possible despite the profound physiologic alteration brought about by surgical intervention.

*Function.*—After a study of the literature and of his own cases of disturbed vesical function in cases of cerebral disease, Schubert<sup>59</sup> reached the following conclusions: There are cortical and subcortical vesical centers in the brain. The cortical center lies bilaterally in the lobulus paracentralis near the center which controls the foot. Its fibers run with the pyramidal fibers toward the spinal cord. The subcortical center lies on both sides of the third ventricle in the hypothalamus and can act independently on the bladder. There are probably no vesical centers in the cerebellum. The type of vesical dysfunction (incontinence or retention) is independent of the seat of the lesion; the duration is longer in cases of bilateral cerebral lesions. The cause of the cerebral lesions may be trauma, tumor or apoplexy or, more rarely, chronic degenerative and inflammatory processes.

*Reconstruction.*—Gironcoli<sup>60</sup> attempted the construction of a new bladder from the cecum in 4 cases of carcinoma of the bladder. His experience was discouraging. Three patients died after the operation; the fourth enjoyed five years of good health and then died from uremia

59. Schubert, H. O.: Ueber Blasenstörungen bei cerebralen Erkrankungen, Ztschr. f. urol. Chir. u. Gynäk. 43:527-539 (Dec. 22) 1937.

60. de Gironcoli, F.: Ueber die kontinente Darmblase, Ztschr. f. Urol. 31: 652-658 (Oct.) 1937.



caused by ascending urinary infection. Gironcoli, in discussing his experience, stated:

The construction of an intestinal bladder is a serious operation, serious in itself and the more so because it is done usually on cachectic patients. To reduce risk, the operation is done in stages. By this method of multiple operation, much time is lost and the patients suffering from carcinoma of the bladder become more and more cachectic, as they derive no benefit from the preparatory operations. Even when a well functioning intestinal bladder is constructed, the patient may die from infection of the urinary tract.

#### URETHRA

*Tumor.*—Mortensen<sup>61</sup> reported a case of carcinoma of the male urethra. The rarity of the condition, coupled with the inaccessibility of the usual site of its occurrence, that is, the bulbous urethra, renders early diagnosis extremely difficult. In addition, the lesion almost invariably is grafted on some more chronic and more frequent lesion in this situation.

Histologically, carcinoma of the urethra must be distinguished carefully from carcinoma arising in the penis, the prostate gland or Cowper's gland and also from secondary involvement of the urethra from these regions. A large percentage of urethral carcinomas are of the squamous cell type, the occurrence of which in a site normally lined by transitional epithelium is explained by the process of epithelial metaplasia. The frequent occurrence of pathologic changes in epithelium leading to the development of leukoplakia, discovered in routine urethroscopic examination for the diagnosis and treatment of chronic urethral infections, stresses the importance of this factor. The papillary type of tumor is found less frequently; it is often observed in younger patients, with whom it is of more rapid growth and of greater malignancy. True adenocarcinoma of the urethra has been described on only 2 occasions. It arises from the glandular structures of the urethra.

In most cases the results of treatment are poor, and in by far the greater number of cases reported the patient has died shortly after diagnosis has been made, whether or not surgical intervention was employed.

Harbach<sup>62</sup> stated that primary carcinoma of the male urethra is of a low degree of malignancy, is slow to metastasize and, owing to its situation, is particularly suitable for resection. It is apparently a disease of middle age, although Paton reported its occurrence in a youth aged 18 and Kroiss in a man aged 91. The chief difficulty is in diagnosis, and

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61. Mortensen, H.: Carcinoma of the Male Urethra, with Report of a Case, *Brit. J. Surg.* **24**:669-675 (April) 1937.

62. Harbach, F. O.: Primary Carcinoma of the Male Urethra, *J. Urol.* **38**: 311-315 (Sept.) 1937.

in practically all cases the diagnosis has been made late, often too late for any hope of cure. The rarity of the disease is proved by the fact that in the past hundred years only about 100 cases have been reported.

The majority of patients have a history of some form of chronic urethral irritation. A history of trauma is frequent. Rizzi in a study of 52 cases found a history of gonorrhea in 60 per cent and a history of trauma in 10 per cent. Trauma and long-continued chronic urethral irritation must be considered etiologic factors. The growth appears most often in the perineal or membranous portion of the urethra and much more rarely in the penile portion. Legueu cited the incidence as 63 per cent in the perineal portion of the urethra. The symptoms are those of pathologic change in the lower part of the urinary tract. Every case of urethral fistula and stricture should be regarded as a potential case of urethral carcinoma.

Operation offers the best chance of cure. If the growth is situated in the penile portion, partial amputation may be done with success, but one must be certain that carcinomatous cells have not been carried posteriorly by the instruments. The presence of tumor in the membranous urethra necessitates complete amputation with transplantation of the urethra. Complete emasculation is not only unnecessary but mutilating. The inguinal nodes should be dissected, but Harbach stated that this procedure should be carried out after a period of rest following amputation of the penis. Infection and sloughing of the inguinal incisions are more likely to occur when amputation and dissection of the nodes are performed simultaneously.

Kreutzmann and Colloff<sup>63</sup> stated that primary carcinoma of the male urethra is a rare disease, only 145 cases, including the 2 which they observed, having been reported.

The treatment which has given the greatest number of cures of carcinoma involving the anterior portion of the urethra is partial or complete amputation of the penis. When the malignant process involved the posterior portion the best results were obtained by resection of the urethra with the growth included. Inguinal adenectomy is advisable in all cases.

*Catheterization of the Ejaculatory Ducts.*—De Assis<sup>64</sup> stated his view on the value of catheterization of the ejaculatory ducts on the basis of 100 cases in which this was done. The procedure is nearly always possible with the help of the new special instruments. Like ureteral catheterization, catheterization of the ejaculatory ducts gives valuable

63. Kreutzmann, H. A. R., and Colloff, B.: The Treatment of Primary Carcinoma of the Male Urethra, *J. A. M. A.* **110**:184-187 (Jan. 15) 1938.

64. de Assis, S.: Klinische Beobachtungen der Samenblase und Samenwege durch den Katheterismus der Ducti ejaculatorii, *Ztschr. f. urol. Chir. u. Gynäk.* **43**:427-451 (Nov. 15) 1937.

information. It is as well fitted for diagnostic and roentgenologic purposes as for therapeutic injections. Of the utmost importance is the systematic study of the seminal vesicles, filled with a contrast medium, before fluoroscopic examination is performed. Such observations indicate whether clinical healing is taking place or whether surgical intervention is necessary.

#### PENIS

*Erythroplasia.*—Dean and Farrow<sup>65</sup> stated that erythroplasia of the penis is a form of erythematous dermatosis which affects the glans and the mucous surface of the prepuce. It is likely that the condition is the result of chronic irritation beneath a tight prepuce. Although the subjective symptoms are usually mild and the lesions appear insignificant, carcinomatous degeneration has been noted in about 40 per cent of reported cases. The microscopic picture is that of chronic inflammatory precancerous dermatosis. The clinical course is characterized by slow but steady extension and by a complete lack of favorable response to treatment with any topical application. In the case reported intense surface irradiation after circumcision was followed by healing. No evidence of relapse was present after more than a year.

*Plastic Restoration.*—Brown<sup>66</sup> reported 4 cases of restoration of the entire skin of the penis. In 3 of the 4 instances, free thick split skin grafts gave permanent healing with complete normal sensation and function. In the fourth case, split grafts were used to supplement scrotal flaps and to repair the defect of the scrotum.

In preparing for the graft the superficial granulation tissue and deep scar tissue are carefully dissected away in layers until the penis can be elongated completely, extreme care being used not to enter either the corpora cavernosa or the urethra. The next most important step is to obtain a free thick split skin graft, of about one-half to three-fourths the thickness of the skin of the thigh, in one piece, large enough to cover the penis completely without the necessity of patching. A catheter is inserted, and an assistant holds the penis completely extended on the catheter. The graft is wrapped carefully and smoothly around the penis, the edges being overlapped to assure complete coverage. It is then sewed accurately in place all around the penis, at the corona and at the abdomen, and then down the line of the overlapping edges, with fine horsehair on fine needles. Fine mesh gauze is wrapped smoothly around the extended penis; a gauze flap is then wrapped securely on with a sterile bandage, so that the penis is held in complete extension on the catheter.

65. Dean, A. L., Jr., and Farrow, J. H.: Erythroplasia of the Penis, *Tr. Am. A. Genito-Urin. Surgeons* 30:405-416, 1937.

66. Brown, J. B.: Restoration of the Entire Skin of the Penis, *Surg., Gynec. & Obst.* 65:362-365 (Sept.) 1937.

The dressing is kept moist with saline solution added through an irrigation tube and is carefully taken off after four or five days. All sutures are removed, dead edges are trimmed away and any blisters or infected regions are opened.

#### TESTICLE

*Tumors.*—Hertzog<sup>67</sup> reported 2 cases of rhabdomyosarcoma of the testis, one of the rarest types of intrascrotal neoplasm. The first case was that of a farmer, aged 35, who had a history of injury to the scrotum in 1921. In 1922 he noticed a small lump in the region of the left testis. This did not increase in size until 1935, when it started to grow gradually. The tumor was removed in 1936, at which time it weighed 1,220 Gm. and measured 17 by 11 by 10 cm. No remnant of the testis or epididymis could be found. The tumor felt firm, but on section a large cystic region was seen, filled with necrotic material. The remaining structure suggested sarcoma. A small portion of differentiated cartilage was present. Microscopic study revealed a tumor composed of striated muscle.

The second case was that of a boy aged 16 who first noticed a slight swelling of the left testis in March 1935. In April 1936 the tumor was removed, at which time it weighed 1,560 Gm. The epididymis could not be found; however, a normal-appearing testis was present. It was entirely surrounded but not invaded by the tumor. No cartilage was present. Microscopically, the tumor was similar to that in the previous case.

*Atrophy.*—Higgins and Cragg<sup>68</sup> exposed white male rats to fumes of carbon tetrachloride for a brief time each day for periods varying from six to twelve weeks. The animals were then examined, and among the changes found was uniform atrophy of the testes and the accessory sex glands, in contrast to uniform enlargement of the adrenal glands. The authors did not endeavor to interpret the significance of these observations.

#### TUMORS OF THE UROGENITAL TRACT

Campbell<sup>69</sup> reported on primary malignant tumors of the urogenital tract; the report was based on the clinical and pathologic study in 77 cases of primary malignant urologic disease, the patients being infants and children whose ages ranged from 3 days to 9 years.

67. Hertzog, A. J.: Rhabdomyosarcoma of the Testis: Report of Two Cases. Proc. Staff Meet., Mayo Clin. 12:570-571 (Sept. 8) 1937.

68. Higgins, G. M., and Cragg, R. W.: Atrophy of the Genitalia and Hyperplasia of the Adrenal Glands of Rats After Breathing Carbon Tetrachloride. Proc. Staff Meet., Mayo Clin. 12:582-584 (Sept. 15) 1937.

69. Campbell, M. F.: Primary Malignant Tumors of the Urogenital Tract in Infants and Children, J. A. M. A. 109:1606-1611 (Nov. 13) 1937.

From 2 to 11 per cent of malignant renal tumors occurring in children are hypernephromas. This type of tumor appears to be more frequent among girls. Hematuria is the dominant early symptom of hypernephroma in children, in contrast to the initial symptom of a mass in the loin, such as occurs with Wilms' tumor. Hematuria or a mass in the region of the kidney will direct attention to the urinary tract, but the diagnosis will rest chiefly on retrograde pyelographic studies.

Embryonal adenomyosarcoma (Wilms' tumor) is the most frequent neoplasm (one fifth of all tumors) of the urinary tract and abdomen occurring in young persons. Seventy-five per cent of Wilms tumors appear before the fifth year of life, and two thirds of them appear before the third year, which is the average age at which the tumors are first recognized. These growths have been observed in the fetus. After the seventh year, hypernephroma is more likely to occur than embryonal adenomyosarcoma.

A fifth of the patients who have Wilms' tumor have metastasis. The spread is characteristically through the blood stream, yet by lymphatic or direct extension the liver, the spleen, the spine, the intestine, the diaphragm and the lungs may be invaded. A tumor in the region of the kidney is the usual early sign of Wilms' tumor. Pain occurs in about 35 per cent of cases of Wilms' tumor. It results principally from capsular tension consequent to the enlarging parenchymal growth. Pain due to mass, weight or abdominal pressure is also frequent. Hematuria occurs late and is present in only about 15 per cent of cases. This is in contrast to its high incidence in cases of renal hypernephroma.

If there is doubt as to the correct diagnosis, a biopsy may be performed on material obtained by aspiration. The center of the tumor mass is determined by triangulation from a study of the urogram, and into this central region a needle (18 gage) attached to a 5 or 10 cc. syringe is plunged. Moderate suction is applied as the needle is introduced, and when it is at the desired depth the suction is increased sufficiently to draw out tissue for microscopic examination.

When only the usual surgical treatment, nephrectomy, is employed, the mortality is about 95 per cent. Only 5 of 55 patients lived longer than one year, a mortality of 91 per cent. The average life expectancy after nephrectomy alone is eight months; recurrences of the tumor are usually found after four months.

Preoperative radiation therapy apparently is a desirable addition in the treatment of this condition. In the employment of irradiation in treatment of the young, due caution must be observed, and vital organs, such as the liver, the spleen and the opposite kidney, must be protected. If the child withstands the treatment well, the total dose may be increased or the therapeutic period prolonged. After preoperative radiation the optimal time for operation appears to be from three to six

weeks. If treated with radiation the tumor becomes greatly reduced in size, but if nephrectomy is not performed within six weeks it recurs, and growths which follow irradiation are less radiosensitive than the original growth; they may even become radiation-fast, and the opportunity for cure may be lost. Beginning three or four weeks after removal of the tumor, a course of irradiation similar to the preoperative course, including irradiation of the regions of metastasis, is employed.

Tumors of the bladder are most unusual among children and are predominantly of mesodermal origin. The symptoms of tumor of the bladder are consequent to obstruction or to neoplastic ulceration. Thus, there are dysuria, frequent voiding and often burning and hematuria. When infection is present the urine is cloudy with pus.

Malignant growths of the penis and the urethra are almost unknown in the young. Urethral polyps are of frequent occurrence in children and merit consideration because they may produce obstruction and may be precancerous lesions.

Approximately 150 cases of tumor of the testicle among children have been reported. Of more than 300 patients treated by Dean for teratoma of the testis, only 2 were children, aged 3 and 4 years respectively. Examination of such growths shows them to be of congenital or embryonal origin; they have been observed at birth. The correct diagnosis of tumor of the testicle is suggested by palpation of a hard or enlarged nodular testis. In palpation of the enlarged testicle squeezing should be avoided, especially when the presence of tumor is suspected, lest malignant cells be forced into the circulation. The prognosis is always poor, and only by the employment of the method outlined in the following paragraph can one hope to reduce the high mortality which now generally exists.

Intensive preoperative and postoperative irradiation should be given in divided doses prior to orchidectomy. This treatment is applied to the local growth, isolaterally to the abdomen and to the lung or other regions in which metastasis has occurred. When the testicular tumor has diminished it may be removed with the region under local anesthesia.

Tumors of the prostate gland are extremely rare and among children are almost exclusively sarcomatous. The symptoms are those of urinary obstruction, often with hematuria and ultimately with chronic complete retention. The diagnosis is made by urologic examination, in which the rectal examination reveals a large mass filling the prostatic region and sometimes compressing the bowel.

Embryologically and endocrinologically the adrenal gland must be considered as intimately related to the urogenital tract. Benign adrenal tumors occasionally are seen post mortem in the young but are seldom encountered clinically except in rare instances of cortical or subcortical

growth, in which cases development of the genital tract and sexual precocity are striking manifestations. The important malignant adrenal tumor among children is neuroblastoma or neurocytoma, and, according to Campbell's observation, it occurs fully a third as often as do malignant renal tumors. Removal of the growth is the proper treatment, but in the case of adrenal tumor, too, intensive irradiation preoperatively and postoperatively, with divided doses, appears to offer the only hope for the reduction of the extremely high mortality.

#### UROLOGIC SURGERY

Priestley<sup>70</sup> stated that in 1936, 841 operations exclusive of transurethral procedures were performed on 758 patients for disease of the genitourinary system. There were 15 deaths in the entire group, or a gross mortality of 1.9 per cent.

Of the 245 patients who underwent operations on the kidney, 5 died, giving a mortality of approximately 2 per cent. Of patients who had operations on the kidney, 116 were operated on for nephrolithiasis. The next most frequent condition which required operation was hydronephrosis. Various changes have been instituted in the general management of nephrolithiasis in the past year. From the surgical point of view, a more thorough effort than ever before is being made to determine whether any obstruction to free renal drainage is present at the same time that stones are removed from the kidney. If obstruction is found, it is corrected when the stones are removed; therefore, plastic procedures now are combined with pelviolithotomy more frequently than in the past. Treatment of the infection which so frequently is associated with nephrolithiasis has undergone decided changes in the last year. It now includes the use of sulfanilamide and its derivatives and the continued use of mandelic acid and nonspecific injections of neoarsphenamine. These methods of treatment have supplanted largely the more cumbersome and difficult ketogenic diet.

Among the 47 patients operated on because of hydronephrosis, nephrectomy was performed on 31 and plastic procedures on the remaining 16. Of 29 patients on whom nephrectomy was performed for malignant tumors of the kidney, preoperative radiation was employed only in treating Wilms' tumor among children. Our experience with preoperative irradiation for adenocarcinoma or hypernephroma of the kidney among adults has not been as satisfactory as that reported by certain authors elsewhere. Among the 64 patients who underwent operation on the ureter there were 3 deaths. Ureterolithotomy was performed in 43 instances without a death. Two deaths occurred following transplantation of the ureter to the sigmoid flexure of the colon.

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70. Priestley, J. T.: Review of Urologic Surgery for 1936, Proc. Staff Meet., Mayo Clin. 12:675-677 (Oct. 27) 1937.

Operation was performed on the bladder in 61 cases, with 6 deaths. Several of the patients who died had advanced carcinomatous lesions of the bladder, and the operation was considered purely palliative. In 40 of the 61 cases operation was performed for carcinoma of the bladder. The operation included excision, electrocoagulation, segmental resection and total cystectomy.

It is interesting to note that of the 752 patients treated for either benign or malignant prostatic hypertrophy in 1936, only 3 underwent perineal or suprapubic prostatectomy; the remainder were treated by transurethral prostatic resection, with gratifying results.

A new procedure for the treatment of hypospadias is being utilized. This entails implantation of a tubular skin graft to form the distal urethra. Although experience with this operation is as yet limited, good results have been reported by the originators of the procedure, and experience at the clinic up to the present time has given promise of gratifying results.

#### TRANSURETHRAL MANIPULATION

Thompson<sup>71</sup> reported on transurethral operations performed in 1936 at the Mayo Clinic. A total of 1,750 patients were subjected to 3,285 diagnostic or therapeutic procedures at the Colonial Hospital during 1936. An anesthetic was given in 1,521 instances. In 763, spinal anesthesia was employed; in 40, general anesthesia, and in 718, intravenous anesthesia. The agent used for intravenous anesthesia was practically without exception pentothal sodium. This drug continues to be satisfactory in urologic work and has been employed more extensively in general surgical practice in the past year.

In 35 cases radon seeds were implanted into tumors of the bladder. In some of these cases other surgical procedures, such as suprapubic segmental resection or some other attack through a suprapubic incision, had preceded the implantation of radon seeds by several months to a year. By this method, small recurrences of neoplasms of grade 3 or 4 occasionally can be controlled satisfactorily.

In 73 cases papillary tumors of the bladder were removed by transurethral methods. Fifty-five patients were subjected to 65 attempts to remove ureteral calculi, and in 54 cases the stone was removed. Litholapaxy was performed in 58 cases, in many of them as a procedure coincidental with transurethral prostatic resection. In 35 cases chronic prostatic abscesses were opened and minor operations were performed on the prostatic urethra to facilitate continued drainage and thus to obliterate the abscess cavities.

71. Thompson, G. J.: Transurethral Surgery in 1936, Proc. Staff Meet., Mayo Clin. 12:809-810 (Dec. 22) 1937.



In 749 cases, 835 resections of the prostate gland were done for benign or malignant enlargement causing obstruction to the flow of urine. It is interesting to note that only 3 per cent of the patients were less than 50 years of age, whereas 14.6 per cent were over 75. The average age for the entire group was 66.

The period of postoperative hospitalization was one week or less in 38.4 per cent of cases and more than three weeks in only 3.1 per cent.

The amount of tissue removed during the course of operation is interesting. In 211 cases it was 25 Gm. or more; in 1 instance 100 Gm. was removed at a single operation.

The mortality rate for the patients who underwent prostatic resection was a little higher than in preceding years. A total of 11 deaths occurred in the series of 749 cases, a mortality of nearly 1.5 per cent. There was no mortality with any of the other procedures.

#### CHYLURIA

Takahasi and Ikeda <sup>72</sup> were able to cure chyluria in a fair percentage of their cases (in all of which the condition was probably caused by filariasis) by simple injections of Ringer's solution into the renal pelvis. In 2 cases catheterization of the ureters alone was sufficient to produce this effect. Patients who were not cured were at least benefited by this treatment, as chyluria ceased for from five days to a year. The authors stated that hyperemia and stasis due to the injected solution or to catheterization tend to destroy the existing fistula between the lymphatic vessels and the renal pelvis. The condition is cured only when it is of recent occurrence; older processes are resistant to this form of treatment.

Wakefield and Thompson <sup>73</sup> reported a series of 5 cases of non-parasitic chyluria. Although more than 100 cases of nonparasitic chyluria have been reported in the literature, a critical review probably would exclude many of them, for only with extreme difficulty can the absence of *Filaria bancrofti* be proved. The diagnosis of nonparasitic chyluria can be made only after one is definitely sure that there has been no chance of exposure to filarial infestation. The voiding of chylous urine is the only symptom of the disorder. Coagulation of the urine before it is voided usually produces discomfort. The malnutrition of the patient can hardly be attributed to the loss of fat in the urine, for the equivalent of 400 calories is an unusually large output.

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72. Takahasi, S., and Ikeda, K.: Heilung der Chylurie durch Nierenbeckeneinspritzung von physiologischer Kochsalzlösung, *Ztschr. f. Urol.* **31**:729-736 (Nov.) 1937.

73. Wakefield, E. G., and Thompson, G. J.: Nonparasitic Chyluria, *J. Urol.* **38**:102-110 (July) 1937.

In the average case, each 100 cc. of urine contains between 500 and 1,000 mg. of fat.

In the 5 cases in Wakefield and Thompson's series, it was possible in only 1 case to visualize the perirenal lymphatics by pyelographic injection of opaque mediums. Subsequent pyelograms in this case showed normal conditions, and the excretion of chylous urine stopped abruptly after the injection of the opaque mediums. There seems to be no reason for discarding either the excretory or the mechanical hypothesis of chyluria, since there is not sufficient evidence to prove or to disprove either. Both hypotheses are theoretically possible. Pyelographic evidence is not sufficient to prove that lymphatic fistulas exist in every case.

#### URINARY ANTISEPTICS

Schulte<sup>74</sup> stated that Domagk deserves credit for the discovery of the value of the azo compounds containing the sulfonamide radical in the para position in the treatment of bacterial infections. Gelmo was the first to mention the drug which is now called sulfanilamide.

The international effort recently directed toward advances in bacterial chemotherapy leaves the clinician armed with sulfanilamide, a drug now in frequent use. However, a previous assumption that this is the pharmacologically effective portion of the molecule and is the chemotherapeutic bactericidal agent is now in question. Recently, investigations have demonstrated the streptococcicidal power of 4-4'-diaminodibenzene sulfone and 4-4'-dinitrobenzenesulfone. Independently and simultaneously Fourneau, Tréfouél, Nitti, Bovet and Tréfouél have proved that 4-4'-dinitrodibenzene sulfide and 4-4'-dinitrobenzenedisulfide have a similar property. Of interest is the fact that these drugs are more efficacious when given by mouth than when given by subcutaneous injection.

Gley also has worked with various compounds containing sulfur, and Girard, Ray and Richard, after much experimentation, concluded that sulfoxides, symmetric or asymmetric, containing groups OH, NH<sub>2</sub> or NO<sub>2</sub> in the para position, when administered by mouth, show an extremely high curative activity not only against streptococcic infections but also against experimental gonococcic infections.

Further experimental proof, therefore, must be awaited to decide what is the most pharmacologically effective drug for bacterial chemotherapy.

Helmholz and Osterberg<sup>75</sup> stated in a previous publication that the reaction of the urine has a definite effect on its bactericidal action after

74. Schulte, T. L.: History of the Development of Sulfanilamide (Para Amino Benzene Sulfonamide), Proc. Staff Meet., Mayo Clin. **13**:53-60 (Jan. 26) 1938.

75. Helmholz, H. F., and Osterberg, A. E.: The Effect of  $pH$  of the Urine on the Concentration of Free and Conjugated Sulfanilamide Necessary for Bactericidal Action, Proc. Staff Meet., Mayo Clin. **12**:661-664 (Oct. 20) 1937.

sulfanilamide has been administered by mouth. They found that sulfanilamide is more effective in urine which has an alkaline reaction than in that which is acid. It was observed, too, that sulfanilamide in higher concentrations acts bactericidally in acid urine. The present study was undertaken for the purpose of determining the effectiveness of lower concentrations of sulfanilamide as a urinary antiseptic. Experiments were conducted by adding known quantities of sulfanilamide to samples of urine which contained certain types of bacteria. A comparison of the bactericidal action of free sulfanilamide added to the urine with that of the free and conjugated forms as excreted in the urine after administration of the drug by mouth also was made. It was found that the conjugated form seemed definitely more bactericidal than the free sulfanilamide. The following conclusions were reached:

1. In its free form, concentrations of only 25 to 40 mg. of sulfanilamide per hundred cubic centimeters of urine when added to an alkaline urine act bactericidally; concentrations as low as 25 to 30 mg. when excreted in alkaline urine act bactericidally.
2. The acetylated form of sulfanilamide does not act bactericidally in urine at a  $p_H$  of 7.8 at a concentration up to 200 mg. per hundred cubic centimeters.

#### UROGRAPHY

Stevens <sup>76</sup> stated that excretory urographic study furnishes sufficient data for exact diagnosis in a limited number of cases; in the others it must be supplemented by retrograde injection.

Better visualization of the renal cortex after excretory urographic examination is an important factor in the diagnosis of tumors of the kidney that do not involve or exert pressure on the renal pelvis or calices.

It is impossible to perforate a normal renal pelvis with an ordinary ureteral catheter. Extreme gentleness should be employed in the catheterization and injection of fluid into the renal pelvis when the patient is an infant or a young child. Injury to the kidney and also back flow are frequent during retrograde pyelographic examination.

Filling the kidney pelvis to the point of discomfort is sometimes a dangerous procedure. The principal danger accompanying extravasation into the parenchyma of the kidney and in the various types of back flow is the possible dissemination of infectious material.

Rupture extending through the capsule of the kidney is the most dangerous complication associated with retrograde pyelographic study.

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76. Stevens, W. E.: Roentgenologic Examination of the Kidney with Special Reference to Backflow and Injuries Associated with Retrograde Pyelography. *Tr. Am. A. Genito-Urin. Surgeons* 30:169-182, 1937.

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